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ALEUKEMIC LEUKEMIA AND ATYPICAL LEUKEMOID CONDITIONS

REPORT OF SEVEN CASES INCLUDING ONE OF ACUTE
ERYTHROBLASTOSIS *

HENRY PINKERTON, M.D.

BOSTON

Atypical conditions are frequently encountered that clinically and pathologically appear to be borderline cases, showing various mixtures of the characteristics of the acute infections, the purpuras, the anemias and the neoplasms of the blood. The literature relating to these unsatisfactorily classified conditions has become formidable, and one is led rapidly from a consideration of atypical cases of leukemia and pernicious anemia to such seemingly unrelated conditions as Mikulicz' disease (Hannema¹) and mycosis fungoides (Fraser²). Attempts have been made to identify some of these conditions with the leukemias and to separate others from this group and further subdivide them into definite entities. Clinically, they show the greatest diversity. From the pathologic point of view, they shade off into the true leukemias by almost imperceptible degrees. It would seem that a satisfactory classification can be made only when etiologic facts are learned.

The term aleukemic leukemia is commonly applied to an ill-defined group of cases in which the blood picture during life shows severe anemia but does not justify the diagnosis of leukemia, while at autopsy, in addition to leukemia-like cellularity of the bone-marrow, accumulations of myeloid or lymphoid cells are found in the viscera, these accumulations having a qualitative, but usually not a quantitative similarity to

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* From the Pathological Laboratories of the Peter Bent Brigham Hospital and the Children's Hospital and the Department of Pathology of Harvard University School of Medicine.

1. Hannema, L. S.: Ein Fall von aleukaemischer Myelose mit dem klinischen Bilde von Morbus Mikulicz, *Folia haemat. Arch.* **32**:116, 1926.

2. Fraser, J. F.: Mycosis Fungoides; Its Relation to Leukemia and Lymphosarcoma, *Tr. Sect. Dermat. & Syphilol., A. M. A.*, 1925, p. 233.

3. Leube, H.: Leukanamie, *Deutsche Klin.*, vol. 3, Diagnostik d. inn. Krankh. Lief. 42, p. 177; cited by Sternberg in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 1.

those found in the true leukemias. (The terms leukanemia³ and pseudoleukemia⁴ were formerly applied to such conditions.)

The occurrence of foci of myeloid cells in the viscera, in response to extensive destruction of the marrow (as by metastatic carcinoma), has long been recognized, and the question naturally arises whether some of the conditions in which anatomic observations lead to a diagnosis of aleukemic leukemia may not be explained in a similar manner, on the basis of abnormal regenerative activity of the hematopoietic system.

The situation is further complicated by the fact that in a great many cases of true leukemia leukopenia spontaneously develops as a terminal event, or at any other time during the course of the disease (King⁵). Furthermore, many cases commonly diagnosed as acute myelogenous leukemia may never show an increased white cell count (King,⁵ Galland,⁶ Sternberg⁷). The possibility of latent chronic leukemia must be excluded in these cases, and this has often been done.

In such cases, the clinical diagnosis must be based on the immaturity of the circulating granulocytes. Since Krumbhaar,⁸ Herz⁹ and others have shown that a high percentage of myelocytes and myeloblasts may be present in the blood stream in cases of severe sepsis, it is obvious that the diagnosis cannot be made from the blood smear alone. If recovery takes place, the diagnosis of acute leukemia is usually not adhered to, although cases of this sort have been reported as acute leukemia with recovery (Gutmann¹⁰). If death occurs and an autopsy is not done, the diagnosis remains doubtful. Cases are on record, however, in which, even with a complete autopsy, sepsis of one sort or another has been so obvious that the writer has been tempted to regard the leukemoid infiltration of the viscera as a terminal event, secondary to the infection (Krumbhaar,⁸ Sternberg¹¹). The visceral infiltration in these cases was, as far as can be learned, always quantitatively less than that typically found in true leukemia, but was sometimes (as in case 7 of the series

4. Cohnheim: Virchows Arch. f. path. Anat. **33**:451, 1860.

5. King, J. J.: Aleucocythaemic Leukemia, Bull. Johns Hopkins Hosp. **28**: 114, 1917.

6. Galland, G. L.: Difficulties in the Diagnosis of Leukemia, Brit. M. J. **2**: 108, 1925.

7. Sternberg, C.: Blutkrankheiten, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 1.

8. Krumbhaar, E. B.: Leukemoid Blood Pictures in Various Clinical Conditions, Tr. A. Am. Phys. **41**:343, 1926.

9. Herz, A.: Infektionen mit leukämischen Blutbild, Wien. klin. Wchnschr. **39**:835, 1926.

10. Gutmann, B.: Leukemia; Report of an Atypical Case, Am. J. M. Sc. **167**: 718, 1924.

11. Sternberg, C.: Ueber acute Leukaemie, Wien. klin. Wchnschr. **33**:553, 1920.

reported here) equal to that found in cases which, because of their idiopathic nature, have been classified as aleukemic leukemia.

The close association of certain types of leukemia with infection has been repeatedly emphasized. The definitely infectious nature of leukosis in the hen (Ellerman¹²) and in the guinea-pig (Snyders¹³), the positive bacteriologic observations in cases of presumably typical acute myeloblast leukemia in man (Sternberg,⁷ Catsara¹⁴ and others) and the evidence adduced by such conditions as infectious mononucleosis¹⁵ and its close relative agranulocytosis (Schultz¹⁶) all strengthen this point of view. Sternberg⁷ and others, in fact, sharply separate most acute leukemias from the group of leukemias in general, on the ground that they are acute infectious diseases. (Sternberg recognizes true chronic leukemia with leukopenia and uses the terms leukopenic and lymphopenic leukemia for such cases). Lubarsch similarly suggests a division of the leukemias into primary (cryptogenic) and secondary, these adjectives having the same significance as in their application to the anemias.

The more specific terms, aleukemic myelosis and lymphadenosis (Naegeli), have been used to separate the myeloid forms of aleukemic leukemia from the lymphoid forms. Rare cases of the myeloid type have been described (Jaffé¹⁷), in which the blood picture constantly shows not only a normal or a low white cell count, but a normal differential count, immature granulocytes being practically absent. Jaffé would restrict the term aleukemic myelosis to these cases, and prefers the term aleukocythemic leukemia for those cases in which immature forms are present in the blood stream in definite and constant numbers. In view of the readiness with which myelocytes and myeloblasts appear in the blood stream in septic conditions, it seems hardly justifiable to separate these cases from otherwise similar cases (case 1 of the series reported below) on this basis alone.

The eight cases to be reported here have been encountered among the routine postmortem examinations at the Peter Bent Brigham Hospital and the Children's Hospital. They have been classified in the following manner: aleukemic leukemia (myelogenous), cases 1 and 2; aleukemic leukemia (myeloblastic), cases 3, 4 and 5; erythroblastosis (acute aleu-

12. Ellerman, V.: *Leucosis of Fowls and Leukemia Problems*, London, Gyldendal, 1921.

13. Snyders, cited by Lubarsch in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 1, p. 666.

14. Catsara, J.: Beitrag zur Frage über die infectiose-toxische Natur der Leukaemischen Erkrankungen, *Virchows Arch. f. path. Anat.* **249**:43, 1924.

15. Baldridge, C. W.; Rohner, F. J., and Hansmann, G. H.: Glandular Fever (Infectious Mononucleosis), *Arch. Int. Med.* **38**:413 (Oct.) 1926.

16. Schultz, W.: Ueber eigenartige Halserkrankungen; Monozyten Angina, *Deutsche med. Wchnschr.* **48**:1495, 1922.

17. Jaffé, R. H.: Aleukemic Myelosis, *Arch. Path.* **3**:56 (Jan.) 1927.

kemic), case 6; leukemoid visceral infiltration secondary to sepsis, case 7, and splenic anemia, eventually (after seven years) appearing as myelogenous leukemia, case 8.

A comparative study of these cases was undertaken, and they are reported in order to bring out their general similarity from the anatomic point of view, and their clinical diversity.

Acknowledgment should be made of the helpful criticism of Dr. S. B. Wolbach, under whose supervision these cases were studied.

REPORT OF CASES

CASE 1.—History.—A man, aged 52, entered the hospital complaining of pain and soreness in the joints of the arms and the legs. This pain began four and a half months before entry, and was almost constantly present following that, but with numerous acute exacerbations. During these severe attacks, he felt feverish and on several occasions had definite chills. He lost 20 pounds (9 Kg.) in weight after the onset of his illness. He had previously been strong and well with the exception of an isolated attack of pain and swelling in the joints of his right arm at the age of 22, which lasted for four weeks.

Examination and Course of the Disease.—The results of the physical examination were essentially negative. During the ten weeks that followed (up to the time of the patient's death) there was a sharp daily rise in temperature (often to 105 F.). Typhoid fever, endocarditis and malaria were considered as diagnostic possibilities, but the Widal reaction was negative, malarial parasites were not found in the blood stream and repeated blood cultures (aerobic and anaerobic) were negative. Repeated examination of the blood during the ten weeks of observation showed an increasing anemia (the count of red cells falling steadily from 3,120,000 to 1,116,000) and a constant leukopenia (the count of white cells ranging from 3,900 to 6,500). The differential count was essentially normal except for the presence of from 4 to 6 per cent myelocytes and of from 1 to 2 per cent nucleated red cells.

Postmortem Examination.—Postmortem examination was made thirteen hours after death. Petechial hemorrhages were noted on the chest, the thorax and the arms. The bronchial and the mesenteric lymph nodes were slightly enlarged, the largest being 1 cm. in its greatest dimension. The spleen weighed 690 Gm., and was flabby. On section, the normal markings were obscured, and the pulp was soft and reddish purple in color. The esophagus showed several areas of ulceration in its lower half; otherwise the gastro-intestinal tract was normal. Peyer's patches and the solitary lymph follicles were not unusually prominent. The liver weighed 2,190 Gm. and was considered to be somewhat enlarged. It was normal in consistency, and the markings were fairly prominent, but leukemic infiltration could not be made out in gross. The bone marrow in the femur, the ribs, and the right clavicle was markedly hyperplastic and ivory white. In different regions, it varied in consistency from soft to moderately firm (the consistency of normal spleen).

Microscopic Examination.—**Bone Marrow:** There was marked hyperplasia, and almost complete replacement of the normal constituents by atypical cells, so that the tissue was almost unrecognizable. An outstanding feature was the presence of large numbers of giant cells, some of which contained each a great many apparently separate nuclei, and others of which appeared to contain each a single multilobulated gigantic nucleus. These large single nuclei were either swollen and edematous in appearance, or hyperchromatic and irregular in outline. The nuclei of these cells were composed of a delicate chromatin network. Their

cytoplasm was irregular in shape and usually homogeneous, and it varied in its staining reaction from eosinophil to basophil (fig. 1). Occasionally, these cells contained phagocytosed erythroblasts, or cells resembling polymorphonuclears.

In addition to the giant cells, many single cells were present. These cells were polygonal or elongated in shape and had each a large round or oval nucleus, composed of finely divided chromatin (resembling the nucleus of a megaloblast) and a moderate amount of stippled or reticulated (basophil or eosinophil) cytoplasm. These cells, except for the difference in size, were similar to many of the giant cells, and the impression was strong that they were fundamentally the same type of cell, probably hypertrophic reticular cells or endothelial cells. The giant cells occasionally showed the cytoplasmic differentiation characteristic of the megakaryocyte. A few myelocytes and nucleated red cells were present, but adult granulocytes and

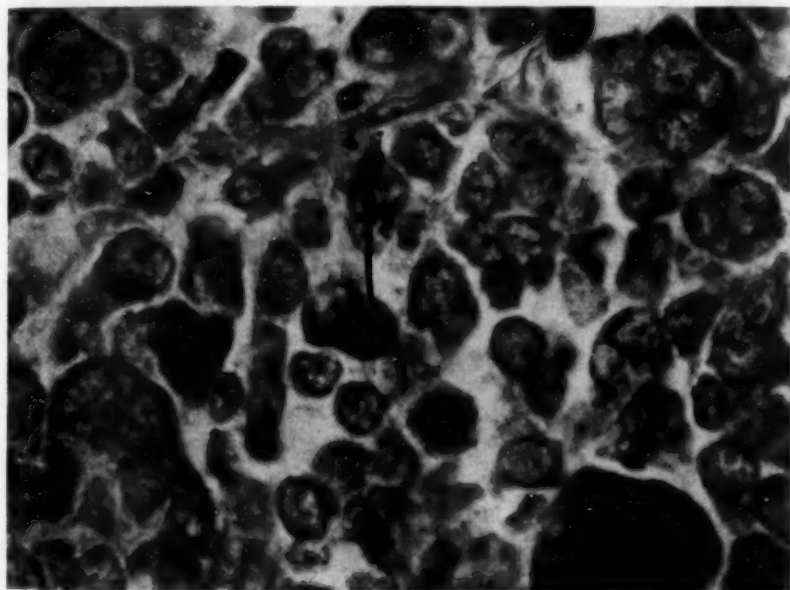


Fig. 1 (case 1).—A high magnification of the bone marrow in a case of aleukemic myelogenous leukemia (giant cell type). Large atypical single and multinucleated cells of a primitive type may be seen. One characteristic mitotic figure is shown. Phosphotungstic acid-hematoxylin stain; $\times 1,200$.

erythrocytes (except within blood vessels) were practically absent. Blood vessels recognizable as such were few in number, and there were many areas of definite fibrosis (fig. 2). Mitotic figures were numerous, and the resemblance to tumor tissue was, in many areas, striking, and the tissue would have been so regarded except for its weak powers of invasion.

Heart: Several of the smaller vessels were apparently plugged with cells resembling early myelocytes.

Lungs: There was marked edema, and a few petechial hemorrhages were seen. Beneath the pleura and in the peribronchial tissue, there were several small areas of fairly dense connective tissue formation. In these areas there were numerous gigantic cells, with irregular, swollen or hyperchromatic, multilobulated nuclei. These cells were frequently undergoing multiple mitosis.

In addition to these large cells there were many smaller cells with basophil cytoplasm, having the appearance of myeloblasts or early megaloblasts, a few definite myelocytes and an occasional island of nucleated red cells. The frequency of mitotic figures gave evidence of the proliferation of these cells in situ. They appeared to be developing from undifferentiated local mesenchymal elements, but it is of course possible that their progenitors may have been metastatic from the marrow. The appearance of these pleural and peribronchial foci was strikingly similar to that of the bone marrow in this case.

Spleen: The pulp was cellular, and the trabeculae were widely separated. The malphigian corpuscles were not seen. The reticular spaces were distended with myeloid cells, including undifferentiated elements, myelocytes, nucleated red cells and many atypical gigantic cells, so that this tissue, also, had much the same appearance as the bone marrow. Mitotic figures were numerous, especially in the elongated cells lining the reticular spaces. There were moderate hemosiderosis and moderate diffuse fibrosis.

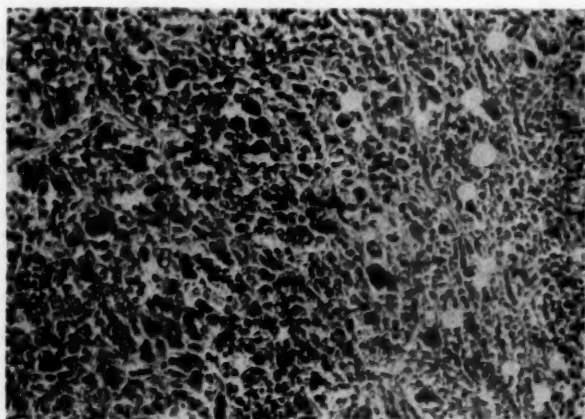


Fig. 2 (case 1).—A low magnification of marrow from the femur in a case of aleukemic myelogenous leukemia (giant cell type). Giant cells and fibrosis may be seen; eosin-metheylen blue stain; $\times 160$.

Liver: The sinusoids contained scattered cells (occasionally in small clusters). Many nucleated red cells were present, as well as myelocytes, myeloblasts and atypical giant cells. Except for the atypical nature of many of the cells, the picture bore a striking resemblance to that of hematopoietic activity in the liver of a newly born infant. The portal areas contained only a few lymphocytes.

Lymph Nodes: Sections of mesenteric, retroperitoneal and bronchial nodes all showed myeloid activity similar to that observed in the spleen. Nucleated red cells were numerous. There was considerable fibrosis in some sections. The surrounding fatty tissue had undergone myeloid transformation in focal areas, and here atypical giant cells were especially numerous (fig. 3).

Esophagus: The usual changes characteristic of an acute ulcer were found.

Bacterial Stains: Organisms could not be demonstrated in sections of the various organs stained by the Giemsa method. Ziehl-Neelsen stains did not reveal acid-fast rods or granules.

Diagnosis.—Hyperplasia and anaplasia¹⁸ of the bone marrow; myeloid metaplasia of the spleen, liver and lymph nodes; fibrosis of the bone marrow, spleen and lymph nodes; anemia; splenomegaly; hepatomegaly (slight); esophageal ulceration; petechial hemorrhages of the lungs, pleura, and pericardium; edema of the lungs, and aleukemic myeloid leukemia (giant cell type).

CASE 2.—History.—A man, aged 61, who had always been in good health except for typhoid fever at the age of 37, entered the hospital complaining of weakness and pallor. Thirteen months before admission he had had whooping cough. From this time, he felt that he had never recovered his full strength. Five months before entry he first noticed definite weakness and pallor, and at about the same time petechial hemorrhages appeared on his legs. It was thought that he had pernicious anemia, and three transfusions were done, which were followed with slight temporary improvement.

Examination and course of the disease.—There was marked pallor, without, however, loss of weight. Recent and old retinal hemorrhages were noted. The edge of the liver was palpable, but the spleen could not be felt.

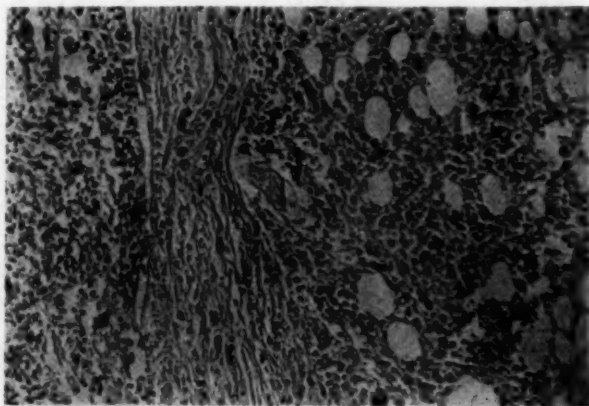


Fig. 3 (case 1).—A peripheral sinus and capsule of a lymph node (in the left third of the figure) and adjacent mesenteric fat (at the right). Note the atypical myeloid reaction in the mesenteric fatty tissue, and the resemblance of this tissue to hyperplastic bone marrow. Several giant cells are present; eosin-methylene blue stain; $\times 160$.

The patient was under observation (except for an interval of about seven weeks that he spent at home) for the four months preceding his death. During this time, he occasionally showed a slight rise in temperature, which was never higher than 100 F., except for a terminal rise to 102. Purpuric spots appeared on the legs on two occasions. In spite of a diet rich in liver, the anemia became more severe, and he died rather suddenly, complaining of pain in the right side of the chest.

Examination of the blood made at intervals during the four months' observation showed a constant leukopenia (the count of white cells ranging from 2,100 to 2,500) and a normal differential count, except for the appearance of 2 per cent

18. This term is used to signify the extensive replacement of the normal constituents of hyperplastic marrow by primitive, undifferentiated elements.

myelocytes in the last count, 48 hours before the patient's death. During this period, the count of the red cells fell from 3,000,000 to 1,500,000, and from 10 to 12 per cent normoblasts were frequently noted in the differential count. The bleeding and clotting times were normal. The color index was always above 1, and the smear showed a picture similar to that of pernicious anemia. Free hydrochloric acid was present in the contents of the stomach in small amounts.

The differential diagnosis lay between pernicious anemia and aleukemic leukemia, and the latter diagnosis was made by the hematologist. It is of interest to note that the failure of the anemia to improve under the therapeutic administration of liver was considered a possibly important point in ruling out pernicious anemia.

Postmortem Examination.—Postmortem examination was made six hours after death. The body was well developed and well nourished. The skin was smooth and pale. The subcutaneous fat was lemon yellow. The mesenteric, retroperitoneal, bronchial, cervical and inguinal lymph nodes were not enlarged. The heart weighed 440 Gm. Petechial hemorrhages were noted on the epicardium.

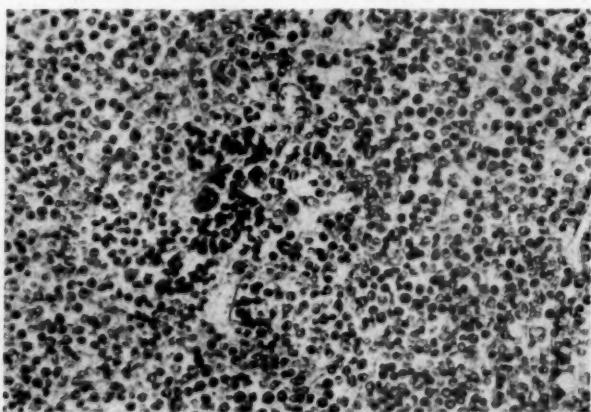


Fig. 4 (case 2).—A low magnification of marrow from the femur in a case of aleukemic myelogenous leukemia. Uniform primitive cell hyperplasia and one island of erythroblasts may be seen; eosin-metheylen blue stain; $\times 160$.

The pleural cavities each contained about 300 cc. of clear fluid. The lungs were markedly edematous. The spleen was moderately enlarged (240 Gm.). Its gross appearance was not remarkable. The liver which was enlarged, weighed 2,380 Gm. It was light brown and uniformly mottled with small opaque areas slightly larger than miliary tubercles, which were recognized grossly as areas of leukemic infiltration. The kidneys weighed 200 and 190 Gm., and were not considered abnormal in gross. The bone marrow in the femur and the ribs was markedly hyperplastic, and it filled the marrow space to the exclusion of fatty tissue and bone trabeculae. It was deep reddish purple.

The other organs did not show changes of importance.

Microscopic Examination.—Bone Marrow: The marrow was markedly hyperplastic, the great majority (about 95 per cent) of the cells being undifferentiated elements with rounded vesicular nuclei and scanty, pale, nongranular cytoplasm. The majority of these cells corresponded in appearance to early myeloblasts. There were scattered clusters of somewhat larger cells, with more abundant, bright blue, irregularly stippled cytoplasm. Islands of nucleated red cells were con-

spicuous in some regions, and myelocytes were fairly numerous. Adult red cells were numerous, but adult granulocytes were practically absent. Mitotic figures were fairly numerous. Giant cells of the type previously described in case 1 were present in somewhat larger numbers than the megakaryocytes of active normal marrow. There was slight fibrosis in a few areas.

Spleen: The malphigian corpuscles were reduced in number and small. In some areas there were marked congestion and diffuse hemorrhage. The pulp was cellular, and the reticular spaces were filled with cells of the myeloid series, myeloblasts predominating, with here and there small groups of eosinophil myelocytes. Islands of erythroblasts were also present in some areas. Giant cells were fairly prominent, some of which appeared to be typical megakaryocytes, while others appeared to be atypical cells similar to those seen in case 1. Occasional mitotic figures were present. There was definite fibrosis in circumscribed areas. These

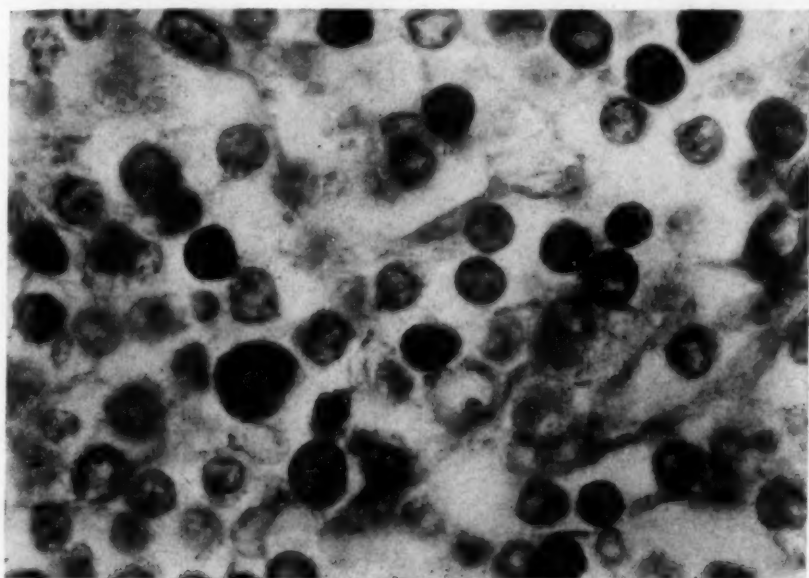


Fig. 5 (case 2).—A high magnification of a portion of the field shown in fig 4; eosin-methylene blue stain; $\times 1,200$.

areas of fibrosis often contained small central vessels, giving the impression that they took origin in malphigian corpuscles. There was marked hemosiderosis.

Lymph Nodes: Sections of bronchial lymph nodes showed myeloid activity similar to that observed in the spleen. The capsules of the nodes showed an increase of connective tissue. The myeloid change in several areas had also extended to the surrounding fatty tissue.

Liver: The miliary nodules described grossly were largely portal in situation. They were so large and numerous that they composed approximately one third of the total substance of the liver. There was evidence of pressure atrophy of the adjacent liver cells. The intervening liver sinusoids contained scattered cells and occasionally small clusters of cells. The Kupffer cells were everywhere prominent. The cells composing these aggregations for the most part resembled myeloblasts or early myelocytes, with a fairly plentiful sprinkling of eosinophil myelocytes and a few nucleated red cells.

Kidneys: Aggregations of cells entirely similar to those seen in the liver were found scattered through the kidney substance, sometimes intertubular, but more often perivascular in location. In the pelvic fatty tissue, also, small islands of these cells were seen, among which were occasional large elongated cells, the appearance of which suggested an origin from primitive mesenchymal cells.

Bacterial Stains: Bacteria were not found in sections of the various organs stained by the Giemsa method, nor could acid-fast rods or granules be demonstrated.

Diagnosis.—Hyperplasia and anaplasia of the bone marrow; myeloid metaplasia of the spleen and the lymph nodes; leukemic cellular aggregations (myeloid metaplasia?) in the liver and the kidneys; anemia; splenomegaly (slight); hepatomegaly, and aleukemic myelogenous leukemia.

CASE 3.—History.—A woman, aged 58, with an unimportant past history, entered the hospital complaining of fever and weakness of one month's duration. The onset was fairly sudden and associated with small tender glands in the back

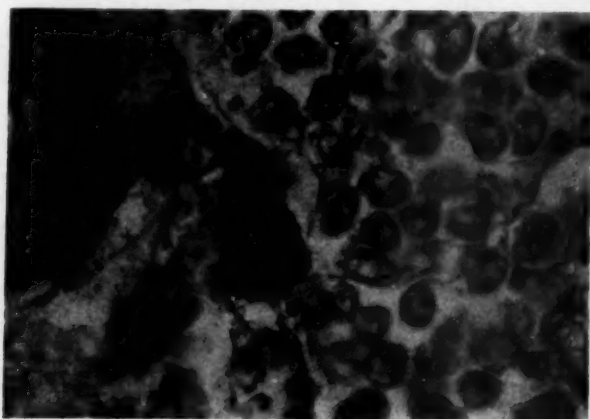


Fig. 6 (case 2).—The edge of a colony of undifferentiated cells in the liver in a case of aleukemic myelogenous leukemia; eosin-methylene blue stain; $\times 1,000$.

of the neck near the scalp line. Herpes labialis developed one week later. One week before entry she was forced to go to bed.

Examination and Course of the Disease.—The results of the physical examination were essentially negative except for slight pallor, and a questionably palpable spleen. Bacteriologic and serologic tests for the typhoid group were negative. Free hydrochloric acid was absent in the fasting stomach contents, but normal after the test meal. The tongue was smooth but not characteristic of pernicious anemia. The white cell count varied from 1,500 to 2,100, but was more frequently near the lower figure. The differential count showed from 80 to 91 per cent lymphocytes and from 8 to 20 per cent polymorphonuclears. Large mononuclears, eosinophils, mast cells and myelocytes were absent. A rare normoblast was seen. The red cell count dropped steadily from 3,120,000 to 1,160,000. The color index was always considerably greater than unity. Anisocytosis and poikilocytosis were striking. A blood culture on entry was negative, but on the day before death a positive culture of *Bacillus pyocyaneus* was obtained. Death occurred one month after entry.

The clinical diagnosis was obscure, but the blood picture was that of pernicious anemia and this diagnosis was made in spite of the atypical acute course, the presence of hydrochloric acid in the stomach contents and the definite suggestion of obscure sepsis. There was a daily rise in temperature (to from 102 to 103 F.) during the entire period of observation, with a terminal rise to 105 F.

Postmortem Examination.—Postmortem examination was made six hours after death. The body was well developed and nourished. The skin showed a yellowish pallor. The spleen weighed 520 Gm. It was soft and deep purple. The liver was normal in size and light yellow. The kidneys were small and irregularly mottled. Bone marrow removed from the femur was markedly hyperplastic and deep red.

Microscopic Examination.—Bone Marrow: The marrow was cellular in appearance (fig. 7 A), and was composed almost entirely of rather small cells with pale, often indented nuclei. These cells were believed to be hematocytoblasts, or primitive blood cells. Differentiated elements were practically absent from the marrow, and only an occasional myelocyte was seen. Rarely, a small island of nucleated red cells was encountered. The striking feature of the undifferentiated cells present in this marrow was their irregularity (fig. 7 B). The nuclei were frequently clover shaped or dumb bell shaped, the cytoplasm conforming to the shape of the nucleus; this appearance suggested that they were in active ameboid movement.

Spleen: There was marked congestion, and the only abnormality that could be made out was the presence in the pulp of large numbers of undifferentiated cells similar to those described in the bone marrow.

Liver: The portal areas were heavily crowded with similar undifferentiated cells (fig. 7 C), and these cells were also scattered through the sinusoids. Quantitatively, the accumulations of abnormal cells were comparable to those seen in true leukemia, although it is to be noted that the liver was not enlarged in gross.

Kidneys: Here again, undifferentiated cells had accumulated between the tubules and around the glomeruli and the blood vessels to such an extent that the appearance was that of a true leukemic infiltration. In the centers of these areas of cellular aggregation, sclerosed glomeruli were frequently seen, but it was not possible to determine whether this condition was secondary to the cellular accumulation or was previously existing and unrelated. These abnormal cells had nuclei that were rather irregular in shape (often elongated or dumb-bell shaped) and composed of a spongelike chromatin network, in which were usually one or more nucleoli. Their cytoplasm was scanty, and it was usually drawn out into long thin processes. Their appearance was similar to that of the hemohistioblasts of Ferrata, as described by Richter.¹⁹ Connective tissue cells of various ages were intermingled with them, and it seemed possible to trace the evolution of the abnormal cells through various intermediate stages back to these mesenchymal elements. A few eosinophil and basophil myelocytes and an occasional small group of nucleated red cells were intermingled with the more primitive cells.

Lymph Nodes: The lymph nodes also showed a marked increase in undifferentiated cells similar to those in the other organs.

Bacterial Stains: Sections of the various organs stained by Giemsa's method were carefully studied. A few clumps of bacilli were found within blood vessels in the liver, but otherwise the results were negative. Stains for acid-fast organisms were negative.

19. Richter, M. N.: Hemohistioblast of Ferrata, Am. P. M. Sc. **169**:336, 1925.

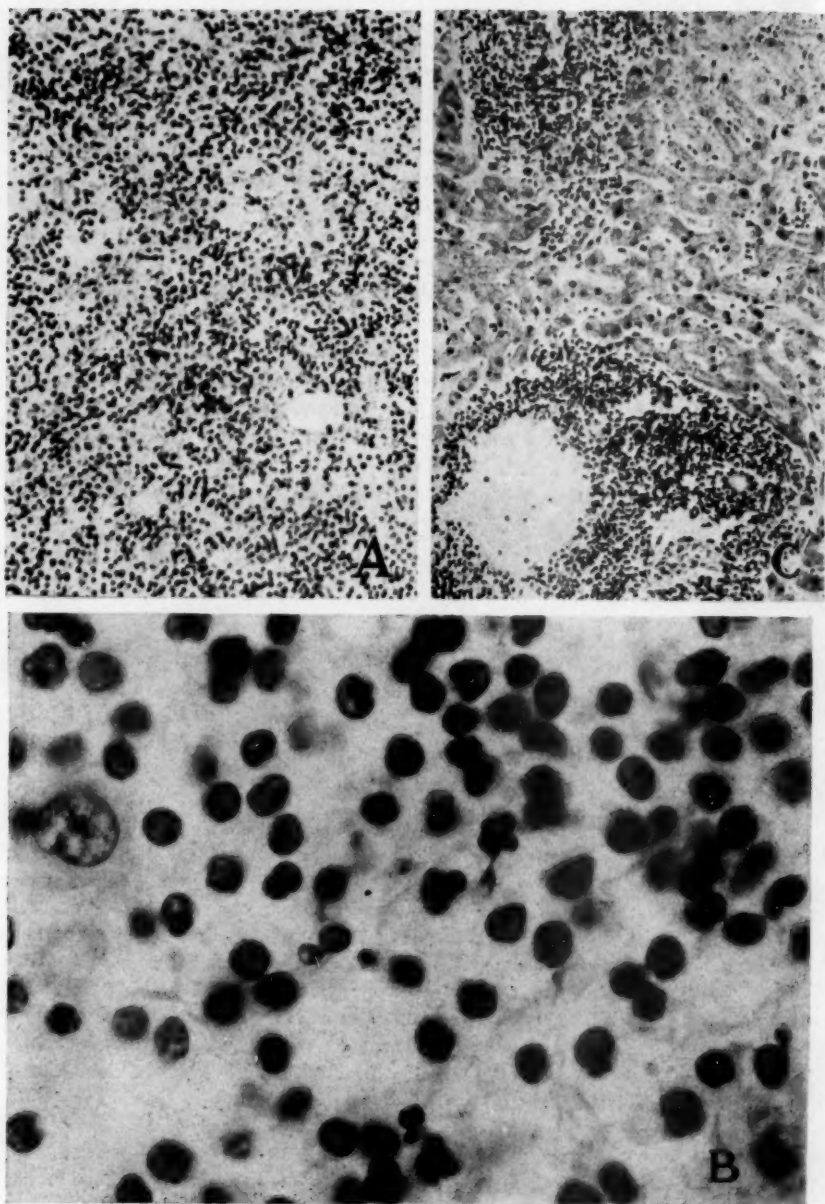


Fig. 7 (case 3).—Aleukemic (myeloblastic?) leukemia. *A* presents a representative view of marrow from the femur showing uniform undifferentiated cell hyperplasia. The cells are small and hyperchromatic; eosin-methylene blue stain; $\times 160$. *C*, portal aggregations of cells in the liver with small collections in the sinusoids; eosin-methylene blue stain; $\times 100$. *B*, a high magnification of the bone marrow showing one large reticulum cell at the left, and many small cells with deeply stained irregularly lobulated nuclei. Adult granulocytes were completely absent and myelocytes extremely difficult to find in this marrow; eosin-methylene blue stain; $\times 1,200$.

Diagnosis.—Hyperplasia and marked anaplasia of the bone marrow; myeloid metaplasia of the spleen, liver, kidneys and lymph nodes; anemia; splenomegaly, and acute aleukemic leukemia ("stem cell" type?).

CASE 4.—History.—A girl, aged 16, entered the hospital complaining of nosebleeds. She had always been well, except for the usual diseases of childhood and an attack of influenza in 1918 (eight years before entry to the hospital). Eight weeks before admission, she began to be attacked with nausea and vomiting (of food just eaten). She became weak, and four weeks before entry began to have profuse nosebleeds, which recurred frequently thereafter. At this time, she had a temperature of 102 F., and a mass in the upper right side of the abdomen. A laparotomy revealed only a large liver.

Examination and Course of the Disease.—The patient was poorly nourished and pale. The liver was definitely enlarged to palpation, but the spleen could not be felt. A few firm, pea-sized lymph nodes were felt in the left axilla and in the groins.

Examination of the blood showed a severe anemia (a red cell count of 1,640,000 dropping to 1,120,000 before death) and leukopenia (the white cell count being from 3,450 to 1,200). The differential count showed from 35 to 50 per cent polymorphonuclears and from 48 to 64 per cent small mononuclear cells, which were considered to be abnormal lymphocytes. A few nucleated red cells were seen, but not any myelocytes. The bleeding time was six minutes and the clotting time one minute. The fragility of the red cells was slightly increased. During the two months of observation there was an irregular fever (to 102 or 103 F. on several occasions). She continued to have nosebleeds and two transfusions gave only slight temporary relief. For one week previous to her death, she complained of severe pain in the region of the enlarged liver.

Postmortem Examination.—This was done eight hours after death. The body was markedly emaciated. Petechial hemorrhages were present over the chest and the abdomen. The mesenteric lymph nodes were moderately enlarged and numerous. The heart was normal, except for petechial hemorrhages on the pericardium. The left lung contained a single small patch of early bronchopneumonia. The liver weighed 2,160 Gm. It was fatty in appearance, and minute nodules of leukemic infiltration could be made out with difficulty. The spleen weighed 150 Gm. It was red and pulpy, but otherwise not remarkable. The kidneys weighed 240 and 220 Gm. They showed subcapsular hemorrhages and a striking nodular leukemic infiltration. The bone marrow from the femur was moderately hyperplastic and red, and had caused some atrophy of the bony trabeculae, but in sharply localized areas it was still fatty in appearance. The other organs did not show important changes.

Microscopic Examination.—Heart: In the pericardial fat there were definite cellular aggregations. These groups of cells were composed largely of medium-sized cells with pale rounded nuclei, but occasional eosinophil and basophil myelocytes and rare nucleated red cells were also present, as well as elongated cells suggesting a mesenchymal origin. The appearance of this fatty tissue was similar to that of early regeneration in fatty bone marrow. Small cellular aggregations of a similar nature were seen in the heart muscle, usually in a perivascular position.

Spleen: There was extreme congestion. The malpighian corpuscles were irregular in size and shape but, on the whole, not increased in prominence. Many of them showed central fibrosis and were nearly obliterated. There was moderate hemosiderosis. The pulp was markedly increased in cellularity, the predominating

cell being consistent in appearance with the lymphoblast or the myeloblast. Myelocytes and nucleated red cells were fairly numerous, however, and mitotic figures were frequently seen.

Liver: The picture was that of central hemorrhage and necrosis, with heavy leukemic infiltration, which was for the most part periportal.

Kidney: The tumor-like nodules described grossly were seen to be areas of dense leukemic infiltration. The cells lay between the tubules (fig. 8, *C*), and mitotic figures were numerous. The cells nearly all had rather large, often indented pale nuclei with a delicate chromatin network and a narrow rim of pale blue staining cytoplasm. It was impossible, on morphologic grounds, to say whether they were myeloblasts, erythrogonia or atypical lymphocytes, but because of the presence of a few typical granular myelocytes they were believed to be early cells of the myelocytic series.

Lymph Nodes: The lymph nodes were cellular in appearance. There seemed to be a uniform filling of the lymph channels with the same cells seen in the other organs. The lymph follicles were everywhere obliterated. Mitoses were numerous.

Bone Marrow: This was hemorrhagic and moderately hyperplastic. Here, as in the other organs, most of the cells were consistent in appearance with myeloblasts, early megaloblasts or abnormal lymphocytes (figs. 8, *B* and *C*). However, islands of fatty tissue alternated with the cellular areas. Islands of nucleated red cells were fairly frequent, while granulocytes were few.

Sections of the other organs did not show changes of importance.

Bacterial Stains: The blood vessels in the heart and the spleen often contained large masses of cocci, and the epithelial cells lining the kidney tubules were often heavily loaded with bacilli. Acid-fast organisms could not be demonstrated.

Diagnosis.—Moderate hyperplasia and marked anaplasia of the bone marrow; leukemic colonization in the liver, spleen, kidneys and lymph nodes; petechial hemorrhages in the pericardium, liver, kidneys and skin; fatty degeneration of the liver; anemia; bronchopneumonia, and aleukemic (myeloblast) leukemia.

CASE 5.—History.—A boy, 3 years of age, previously well, was brought to the hospital because of an increasing pallor of seven months' duration.

Examination and Course of the Disease.—The child was well nourished but apathetic. The results of the physical examination were otherwise essentially negative. The red cell count was 1,096,000, and the hemoglobin 25 per cent. The red cells were almost without abnormalities. The white cell count was 5,500, with 21 per cent polymorphonuclears and 79 per cent lymphocytes, many of which appeared to be abnormal. The blood smear was examined by a hematologist of wide experience, who made a note that it showed an undertermined type of anemia and that, aside from the anemia, there was not any positive evidence of a serious blood disorder. In spite of a transfusion and a diet rich in liver and iron, the anemia became more severe, and four weeks after entering the hospital the child developed air hunger and died. The blood picture, except for the increasing anemia, did not change in any significant manner during the period of observation. There was a slight irregular fever during the period of observation (from 97 to 100.6).

Postmortem Examination.—Postmortem examination was made three hours after death. The development and nourishment were found good. The skin was pale and had a slightly yellowish tinge. Grossly, aside from the anemia, the only important abnormality was observed in the bone marrow. Marrow from the femur was found to be hyperplastic, with atrophy of the bone trabeculae. It was dark pink and soft, but not gelatinous. Marrow from the ribs was a normal deep

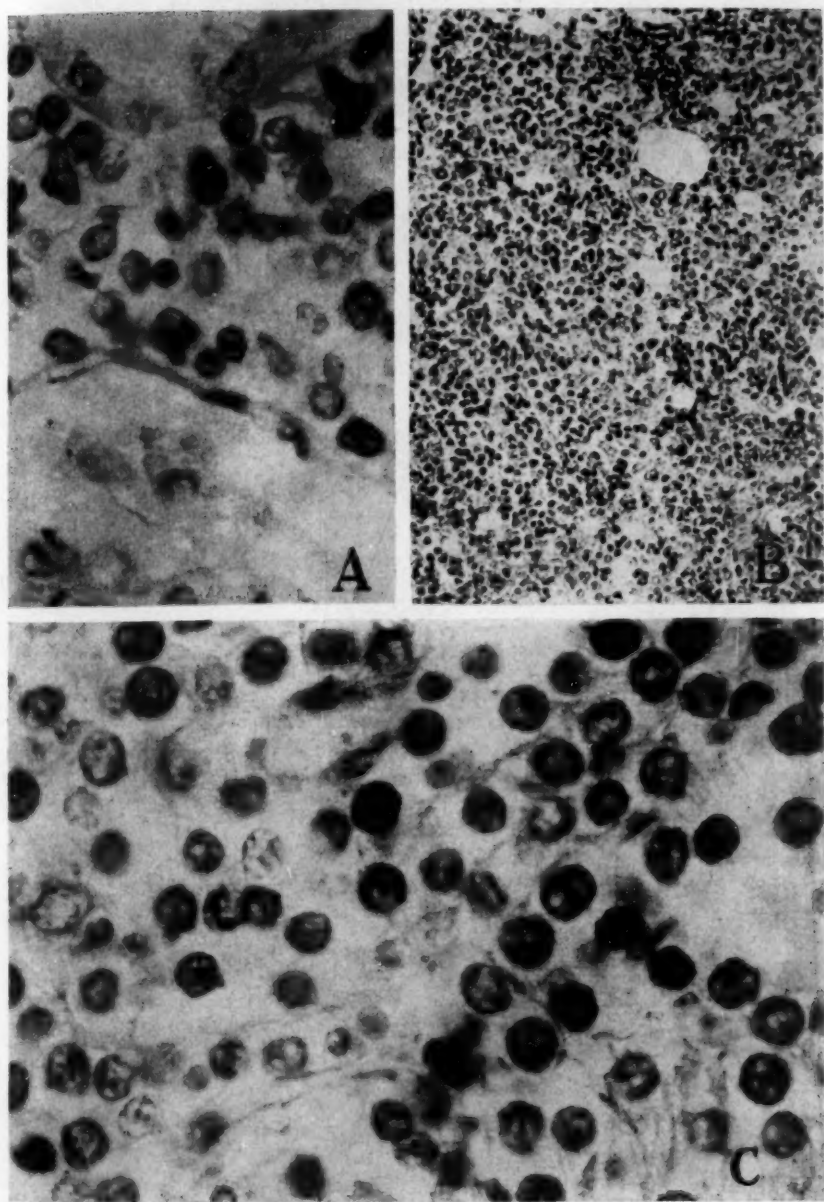


Fig. 8 (case 4).—Aleukemic (myeloblast) leukemia. *A*, a collection of cells between a glomerulus and a tubule in the kidney; eosin-methylene blue stain; $\times 1,000$. *B*, marrow from the femur in a localized area of hyperplasia. The deeply stained cells are mostly nucleated red cells; eosin-methylene blue stain; $\times 160$. *C*, a high magnification of the marrow showing undifferentiated cells resembling large lymphocytes; eosin-methylene blue stain; $\times 1,200$.

red and not noticeably hyperplastic. The mesenteric lymph nodes were slightly enlarged (the largest being 6 mm. in diameter). Bronchial, mediastinal and cervical nodes were not enlarged. The spleen, kidneys, liver, pancreas, lungs, suprarenal gland, bladder and gastro-intestinal tract appeared grossly normal. The prussian blue reaction was strongly positive on the liver and the spleen, but negative on the tissue of the lung and the kidney.

Microscopic Examination.—Bone Marrow: The bone marrow was markedly hyperplastic, being composed chiefly of nucleated red cells and small cells of an unclassifiable nature resembling lymphocytes (fig. 9 A). The cells lacked, however, the typical nuclear structure of the ordinary small lymphocyte, and their nuclei showed much more irregularity of shape (fig. 9 B). They were believed to be of the myeloid series (the so-called micromyeloblasts) rather than lymphoid cells, although the evidence for this view was not complete. Myelocytes were present in moderate numbers. Adult red cells were fairly numerous.

Heart: The heart muscle fibers contained much fat.

Spleen: There was marked hematopoietic activity. The splenic corpuscles were numerous but not prominent, owing to the enormous increase of cells in the pulp. These cells were of four types: elongated cells with abundant cytoplasm (hemohistiocytes?), smaller cells consistent in appearance with myeloblasts or prolymphocytes, small dark cells resembling those described in the marrow and erythroblasts. The relative proportion of the last two types was difficult to determine, but otherwise these four types of cells appeared about equally numerous. Hemosiderin was inconspicuous.

Liver: Marked fatty infiltration was observed about the central veins, but not any leukemic infiltration.

Kidneys: There were definite periglomerular, perivascular and intertubular collections of small unclassifiable cells resembling those found in the marrow (fig. 9 C). Among these cells were definite small clumps of staphylococci, often intracellular. Nucleated red cells were not seen here. The tubular epithelium was uniformly and heavily laden with fat.

Lymph Nodes: These were hyperplastic and their capsules were over-run. The changes were similar to those in the spleen.

Bacterial Stains: Except in the lesions of the kidney (as noted above) bacteria were not found in Giemsa-stained sections of the various organs. Acid-fast stains were negative.

Diagnosis.—Hyperplasia and anaplasia of the bone marrow; myeloid metaplasia of the kidneys, spleen and lymph nodes; fatty infiltration of the heart, liver and kidney; edema of the lungs, and aleukemic (myeloblastic) leukemia (?).

CASE 6.—*History.*—A boy, aged 7½ years, the fourth child of healthy parents, had been well until seven weeks before entry into the hospital; at that time he began to have diarrhea, which became more and more severe. Aside from weakness there had not been other symptoms.

Examination and Course of the Disease.—The results of the physical examination, except for emaciation, pallor, a distended abdomen and slight generalized glandular hyperplasia, were essentially negative. Proctoscopic examination did not reveal any ulcerations of the lower part of the colon. The diarrhea was so severe that ileostomy was considered necessary to save the patient's life, but he died before this could be done (two weeks after admission).

The blood picture on entry showed 31,000 white cells, of which 90 per cent were considered to be atypical small lymphocytes, 9 per cent polymorphonuclears and 1 per cent myelocytes. The white cell count during the next week fell to

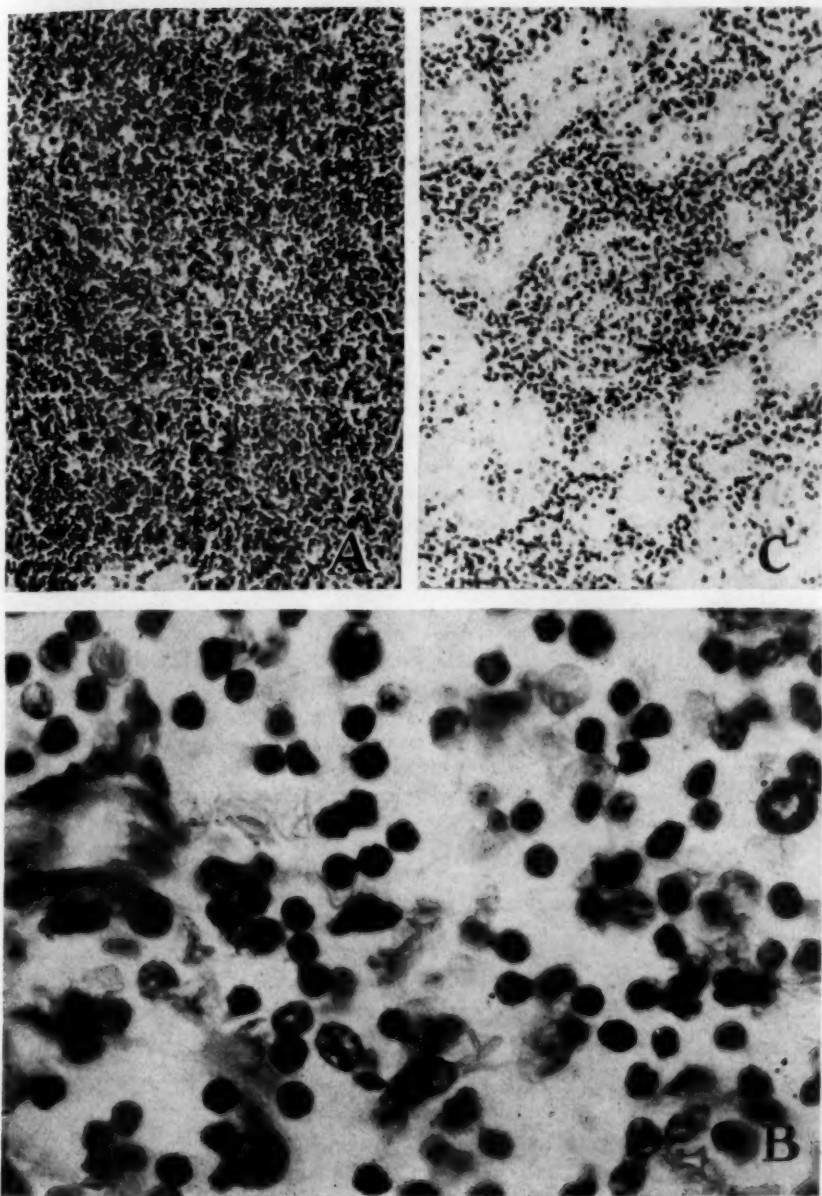


Fig. 9 (case 5).—Aleukemic (myeloblast?) leukemia. *A*, marrow from the femur showing extreme cellularity. The small size of the cells should be noted (compare with fig. 4), which was taken at the same magnification; eosin-methylene blue stain; $\times 160$. *B*, a high magnification of the marrow showing scattered reticulum cells and many small cells with hyperchromatic nuclei, some of which are nucleated red cells, while others are primitive cells of lymphoid appearance (see fig. 12); eosin-methylene blue stain; $\times 1,200$. *C*, periglomerular and intertubular aggregations of cells in the kidney, comparable to those seen in true leukemia; eosin-methylene blue stain; $\times 160$.

11,000, the differential count remaining essentially unchanged, except that 10 per cent myelocytes were found. Further leukocytosis was not observed. The red cell count during this period varied between 3,850,000 and 2,450,000 (hemoglobin being from 45 to 65 per cent). Nucleated red cells were "numerous." Stool examinations and Widal reactions revealed nothing abnormal. The temperature rose to 100 F. on three occasions during the period of observation.

Postmortem Examination.—Postmortem examination was made four hours after death. The body was found poorly nourished. There was a small amount of bloody fluid (75 cc.) in the peritoneal cavity, and the peritoneum was everywhere dull and sticky. Impression smears showed "lymphocytes" and a rare polymorphonuclear, but not any bacteria. The mesenteric lymph nodes were moderately enlarged. The lungs showed early acute bronchopneumonia. The spleen was somewhat enlarged (100 Gm.) and was deep red but otherwise not remarkable. The mucosa of the ileum and of the colon was slightly injected in a few areas, and a small amount of mucinous material was adherent to the surface of the colon. There was not, however, any gross evidence of an important enteritis. The bone marrow was obtained from the second lumbar vertebra only, in which it was dark red but had not caused atrophy of the trabeculae. The other organs appeared normal.

Microscopic Examination.—The pericardium and pericardial fatty tissue contained focal collections of extremely small cells with dark, homogeneous nuclei. Many of these had definite erythrocytoid cytoplasm and were typical erythroblasts.

Spleen: The architecture, on the whole, was not markedly disturbed. The striking feature was the tremendous number of nucleated red cells that this tissue contained. These cells were numerous in the sinusoids, but were especially closely packed together in the trabeculae and the capsule. Both of these structures were consequently difficult to distinguish from the splenic pulp. About half of the nucleated red cells had definite sharp spherical nuclei, while the other half had irregular, shriveled pyknotic nuclei, often showing "clover leaf" or "budding yeast" shapes. Cells similar to these are found in any hyperplastic bone marrow, always mingled with the colonies of well preserved nucleated red cells. This shriveled appearance of the nucleus probably represents the initial stage of degeneration. Nearly all the nucleated red cells of both forms were extremely small and would be regarded as microblasts. In addition to the nucleated red cells there were moderate numbers of larger paler cells resembling megaloblasts, and occasional myelocytes. Hemosiderosis was well marked.

Pancreas: The interlobular and interacinar connective tissue was moderately increased in amount and uniformly and heavily infiltrated with small nucleated red cells, together with moderate numbers of larger, earlier cells of the myeloid series (fig. 10 A). An occasional eosinophil myelocyte was also seen. The connective tissue found in this organ and, in fact, in the other organs as well, showed definite abnormalities. The changes consisted in a swelling and hyalinization of the collagen fibrils, which were collected into bands from 7 to 8 microns in width, in which the individual fibrils could not be distinguished. The significance of this alteration in the intercellular substance is not known.

Liver: There was a considerable increase in the portal connective tissue, and this connective tissue was heavily infiltrated with small cells that, like those present in the other organs, were differentiating to erythroblasts. Rare eosinophil myelocytes were also present.

Gastro-Intestinal Tract: Sections at various levels did not show any evidence of acute colitis. The submucosa and the adventitia showed a moderately heavy

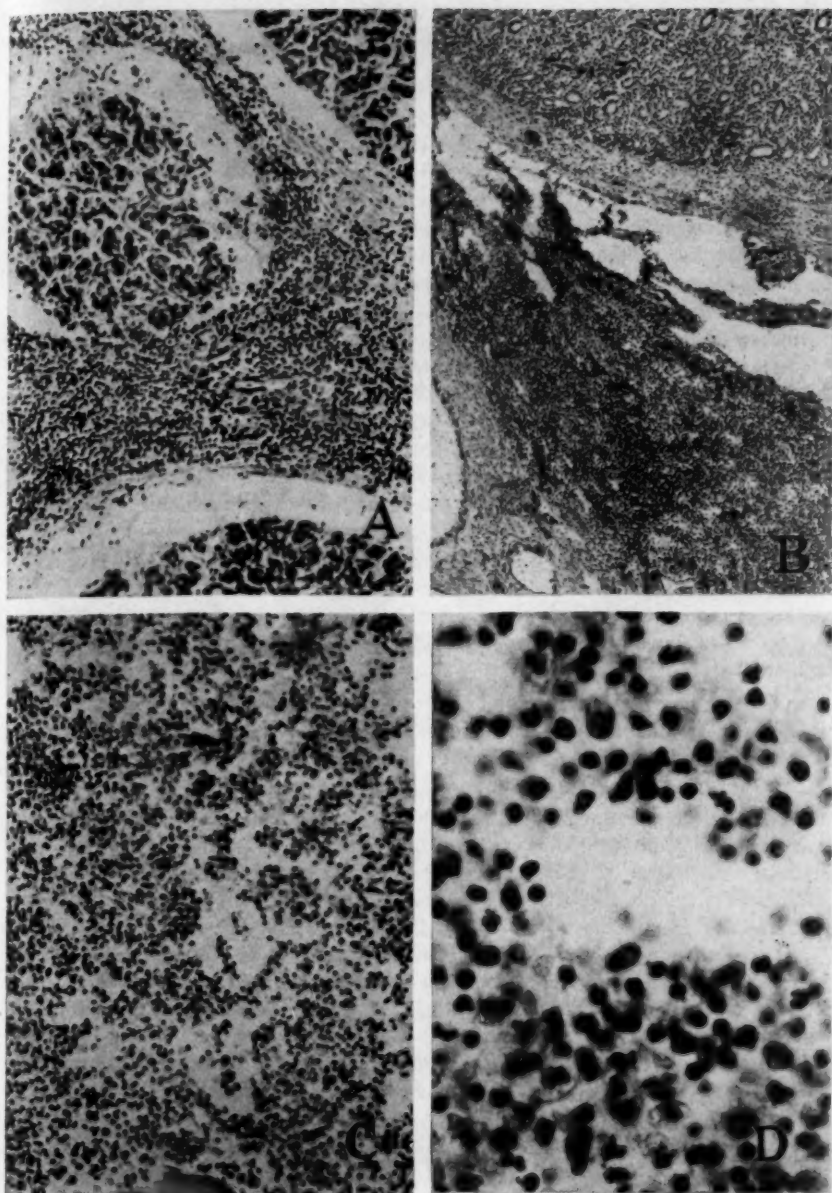


Fig. 10 (case 6).—Aleukemic erythroblastosis. *A*, a low magnification of the pancreas showing marked interlobular fibrosis and a tremendous accumulation of small dark cells, many of which are definitely erythroblasts; eosin-methylene blue stain; $\times 100$. *B*, an erythroblastic reaction in areolar tissue in the pelvis of the kidney. A cross-section of a large branch of the renal artery is shown in the lower left-hand corner, and a kidney tissue in the upper part of the field hematoxylin eosin stain; $\times 40$. *C*, a low magnification of the vertebral marrow showing a preponderance of small, dark, nucleated red cells; eosin-methylene blue stain; $\times 160$. *D*, a high magnification of a representative region in the marrow. About 80 per cent of the cells are nucleated red cells and most of them are small (microblasts); eosin-methylene blue stain; $\times 1,000$.

infiltration with the abnormal cells described. Just beneath the peritoneum these cells were especially numerous.

Kidneys: Heavy infiltration was seen about the blood vessels, in the capsule and beneath the mucosa of the pelvis (fig. 10 B).

Lymph Nodes: The picture was similar to that observed in the spleen. The capsules showed fibrosis and heavy cellular infiltration, which extended out into the surrounding areolar tissue (fig. 12 H).

Bone Marrow: The bone marrow (vertebral) appeared active, and again the great majority of the cells were nucleated red cells (fig. 10 C), although granular myelocytes were more numerous than in the other organs. Adult granulocytes were practically absent. Many of the nuclei of the erythroblasts appeared to be naked, but, on careful examination, were seen to be surrounded by a clear space outlined as a faint cytoplasmic border. Megaloblasts and normoblasts were about equally numerous (fig. 10 D).

Thymus: The picture was similar to that in the other organs, the capsule and the trabeculae showing a particularly heavy infiltration with definite erythroblasts.

Sections of the other organs were essentially without abnormality.

Bacterial stains: Sections stained for bacteria showed a few diphtheroid bacilli on the capsular surface of the spleen and scattered organisms of a similar nature in the bone marrow. No acid-fast rods or granules could be demonstrated.

Diagnosis.—Erythroblastic hyperplasia of the bone marrow; erythroblastic metaplasia of the mesenchymal tissue in the spleen, liver, kidneys, lymph nodes, pancreas, thymus, pericardium and peritoneum; fibrosis of the pancreas, liver and lymph nodes; low grade peritonitis of unknown origin; early acute bronchopneumonia, and erythroblastosis (acute aleukemic).

CASE 7.—History.—A boy, aged 6, entered the hospital complaining of weakness, pallor, perspiration and pain in the legs. He had had whooping-cough at the age of 9 months and chickenpox at the age of 2. From the age of 10 months until two and one-half years before entry into the hospital, he had had frequent attacks of vomiting, sweating and weakness, with diarrhea (followed by constipation) lasting from seven to ten days and recurring about every three months.

Following this he was well for six months, then (two years before entry) he complained of lameness and soreness in both knees. This lasted for one month. Except for pallor, he was then well until nine months before entry; then both ankles became lame and sore, but were not red or swollen. One week later, he had an attack of acute tonsillitis. Thereafter, his joints were intermittently lame, and on several occasions he had a fever of from 100 to 101 F. for several days.

Examination and Course of the Disease.—The body was well developed and nourished but pale. There was a slight thickening of the ankles, knees and elbows. The examination of the blood showed marked anemia (a red cell count of from 2,300,000 to 1,400,000 with hemoglobin from 15 to 50 per cent). The white cell count during the period of observation varied from 5,800 to 1,130. The differential count showed from 60 to 72 per cent small mononuclear cells, which at first appeared to be myeloblasts but in subsequent smears appeared more like lymphocytes. Reticulated red cells were numerous. The blood was studied by an experienced hematologist, who, on the basis of the arthritis, leukopenia and relative lymphocytosis, thought the condition of the blood was secondary to a focus of infection with a toxic effect on the bone marrow. Repeated transfusions gave only temporary relief. After nine weeks' stay in the hospital, during which no focus of infection could be brought to light, tenderness developed over the left fourth and fifth ribs, anteriorly. On exploration, osteomyelitis was found, and shortly

afterward hemolytic streptococci were grown from the blood stream. In spite of intravenous injection of mercurochrome-220 soluble, the patient died two days later. During the patient's stay in the hospital, the temperature ranged irregularly from normal to 104 F.

Postmortem Examination.—Postmortem examination was made six hours after death. The body was well developed and nourished. There were abscesses in the marrow cavities of the fourth and fifth ribs, from which a streptococcus was cultivated. The mesenteric and the retroperitoneal lymph nodes were slightly enlarged. The lungs showed patchy bronchopneumonic consolidation. The spleen weighed 50 Gm. It appeared grossly normal. The entire colon showed an extreme thickening of the walls and a mucosa yellowish brown, with many irregular ulcerations having fibrous bases, often covered by a heavy membranous exudate. The left kidney showed a single small abscess with a contiguous area of infarction. Otherwise the kidneys appeared normal. The aorta showed acute atheromatous changes. The bone marrow in the femur, tibia and ribs was markedly hyperplastic and grayish red. It was firm and almost fibrous in some areas. The left kneejoint contained a glairy mucinous material and there was definite injection and roughening of the articular surfaces. The heart, pancreas, thymus, liver, gallbladder, suprarenal gland and brain did not show changes.

Microscopic Examination.—Spleen: The reticular spaces showed prominent endothelium with frequent mitoses, and contained a few myelocytes and rare nucleated red cells, in addition to the usual cells. The malphigian corpuscles were rather small and widely separated. There was an extraordinary amount of hemosiderin present, and many of the red cells were stained yellowish or green.

Pancreas: Scattered collections of cells were seen in the interacinar connective tissue, the predominating cell being consistent in appearance with the early myeloblast.

Liver: The portal areas were crowded with these same cells (myeloblasts?) and a few similar cells were scattered through the sinusoids. The Kupffer cells were everywhere prominent and occasionally in mitosis.

Colon: The mucosal surface was covered with a thick layer of necrotic exudate, while the wall was cicatrized and fairly heavily infiltrated with inflammatory cells of all sorts, but adult polymorphonuclears were rare.

Lymph Nodes: The mesenteric lymph nodes showed a picture of chronic inflammation with a slight increase in the number of the cells resembling early myelocytes. Lymph follicles were entirely absent.

Kidneys: A section from the left kidney showed an acute abscess, typical in appearance, except for the fact that the polymorphonuclear leukocytes were few in number and often young in appearance. Other sections from both kidneys showed numerous intertubular and periglomerular aggregations of early myeloid cells similar to those described in the other organs (fig. 11 A). Mitotic figures were frequent among these cells.

Bone Marrow: Sections of the marrow from the tibia, femur and ribs all showed marked hyperplasia. The marrow was almost uniformly composed of nongranular cells (fig. 11 B), with only a few islands of erythroblasts and rare eosinophil myelocytes (fig. 11 C). Adult polymorphonuclears were practically absent. Megakaryocytes were fairly numerous but atypical giant cells, like those seen in cases 1 and 2, were not observed. Mitotic figures were numerous. Many sections showed marked fibrosis. Sections of the other organs were essentially without abnormality.

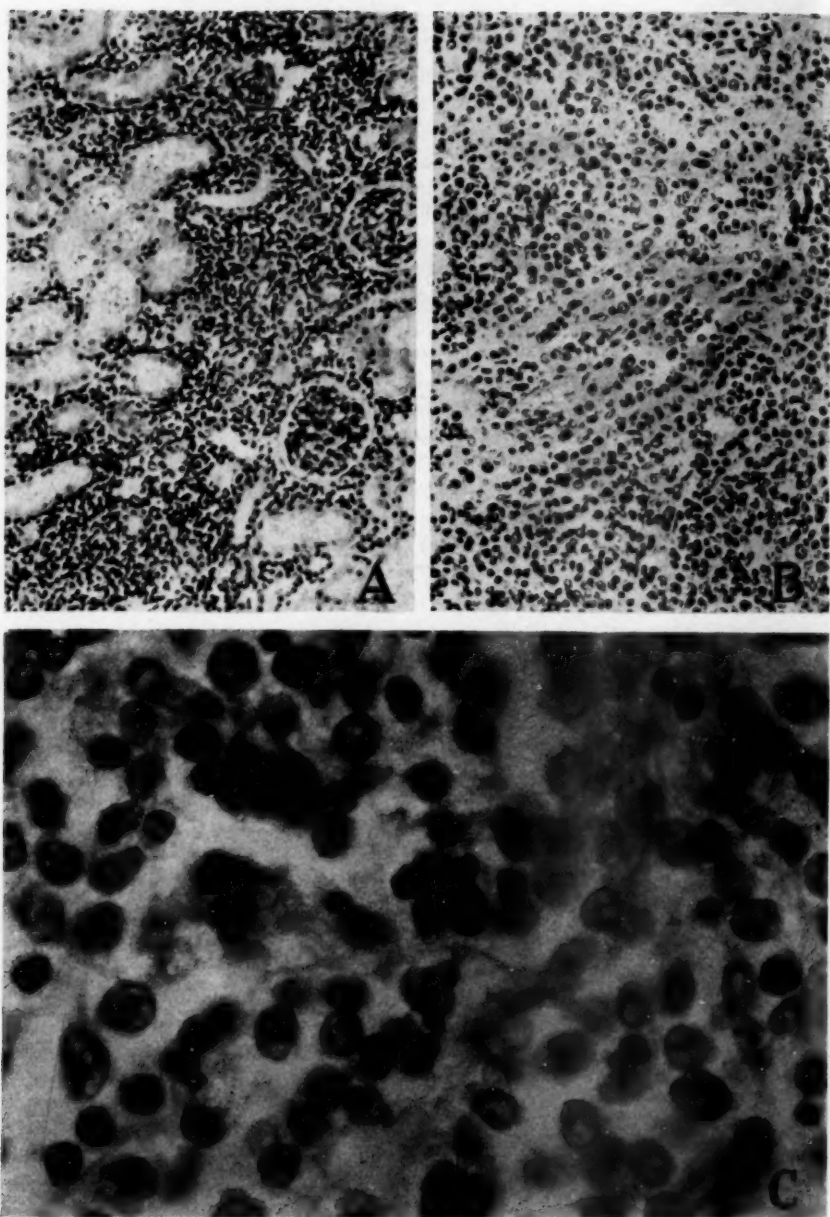


Fig. 11 (case 7).—Prolonged sepsis with leukemoid changes. *A*, a low magnification of the kidney showing leukemia-like aggregations of undifferentiated cells like those in the bone marrow. Anatomically, the picture here is not distinguishable from that of true leukemia; eosin-methylene blue stain; $\times 120$. *B*, a low magnification of the marrow from the femur showing uniform cellularity almost without evidence of differentiation. There is a slight fibrosis; eosin-methylene blue stain; $\times 160$. *C*, a high magnification of the marrow showing a uniform replacement of the normal elements by primitive cells; eosin-methylene blue stain; $\times 1,000$.

Bacterial Stains: In spite of the positive blood culture obtained forty-eight hours before death, bacteria could not be demonstrated in the sections, including those from the abscesses in the kidneys and the ribs.

Diagnosis.—Chronic ulcerative colitis; anemia (severe secondary); osteomyelitis of the ribs; septicemia; abscess of the left kidney (small); bronchopneumonia; marked hyperplasia and anaplasia of the bone marrow; myeloid metaplasia of the liver, kidneys and pancreas; chronic arthritis, and arteriosclerosis (acute).

CASE 8.—History.—A man, aged 52, entered the hospital complaining that he had suffered intermittent pain in the left upper quadrant of the abdomen for five

TABLE 1.—Summary of Clinical Features

Case	Age	Sex	Duration	Fever	Purpura	Blood Picture	Other Clinical Features	Clinical Diagnosis
1	52	M	9 mo.	Picket fence type	+	Severe anemia, leukopenia (4.6%), myelocytes (1.2%), nucleated reds	Joint pains, emaciation	Endocarditis?
2	61	M	9 mo.	Irregular, slight	++	Severe anemia, differential count normal, 10% normoblasts	Nutrition good, no response to liver diet	Primary anemia? aleukemic leukemia?
3	58	F	2 mo.	Septic type	0	Severe anemia, leukopenia, relative lymphocytosis, few normoblasts	Nutrition good, herpes labialis	Acute primary anemia
4	16	F	4 mo.	Moderate irregular	+++	Severe anemia, leukopenia, lymphocytosis, few normoblasts	Severe nose bleeds, vomiting, emaciation	Purpura hemorrhagica
5	3	M	9 mo.	Slight, irregular	0	Severe anemia, leukopenia, lymphocytosis (relative)	No emaciation	Secondary anemia
6	7	M	2 mo.	Slight, irregular	0	Moderate anemia, absolute lymphocytosis, 10% myeloblasts, many normoblasts	Severe diarrhea, emaciation	Ulcerative colitis
7	6	M	4 yr.	Moderate, irregular	0	Severe anemia, leukopenia, lymphocytosis, (relative)	Joint pains, osteomyelitis, nutrition good	Secondary anemia
8	52	M	8 yr.	Moderate, irregular	0	Severe anemia, leukopenia (4%), myelocytes (3%), nucleated reds	No emaciation, no free hydrochloric acid in stomach	Banti's disease? primary anemia?

years. He had previously been well except for typhoid fever at 21 years of age and an acute infection of the upper part of the respiratory tract at about the time the illness in question began.

Examination and Course of the Disease.—Physical examination showed a yellowish pallor, a smooth tongue and an enormous spleen. There was moderate anemia (the red cell count being 3,128,000), and the color index was 1.2. The white cell count was 5,200, and the differential count was normal, except for the presence of 4 per cent myelocytes, 2 per cent myeloblasts and 156 normoblasts per cubic millimeter. Anisocytosis and poikilocytosis were marked. Gastric analysis did not show free hydrochloric acid.

The diagnosis of Banti's disease was made, although it was felt that it was difficult to rule out pernicious anemia and the hematologist was in favor of a diagnosis of aleukemic leukemia.

Splenectomy was done. The spleen weighed 1,403 Gm. Microscopically, the architecture was well preserved and there was marked erythropoietic activity. Nucleated red cells were numerous, but a still more striking feature was the presence of clusters of large cells with rounded, pale vesicular nuclei and bright blue staining, thready cytoplasm. These cells often occurred in what appeared to be syncytial masses. They were believed to be the immediate progenitors of the erythroblasts (erythrogenia). Other primitive cells (presumably myeloblasts) were fairly numerous. The diagnosis made was erythropoietic splenomegaly.

TABLE 2.—Summary of Pathologic Changes

Case	Bone Marrow	Spleen	Lymph Nodes	Liver	Kidneys	Special Features	Pathologic Diagnosis
1	Ivory white, hyperplastic, anaplastic, giant cells	600 Gm., myeloid metaplasia, giant cells	Slightly enlarged myeloid metaplasia, giant cells	2,190 Gm., diffuse myeloid metaplasia	Negative	Myeloid reaction in mesenteric fat and in peribronchial tissue	Aleukemic leukemia (myelogenous)
2	Red-purple, hyperplastic, anaplastic	240 Gm., myeloid metaplasia	Not enlarged, myeloid metaplasia	2,380 Gm., leukemoid aggregations	Leukemoid aggregations	Myeloid reaction in peribronchial fatty tissue	Aleukemic leukemia (myelogenous)
3	Red, hyperplastic, anaplastic	520 Gm., increased cellularity	Not enlarged, increased cellularity	Not enlarged, leukemoid aggregations	Not enlarged, leukemoid aggregations	Small primitive cells, lymphoid?	Aleukemic leukemia (myeloblastic)
4	Hyperplastic, hemorrhagic, anaplastic	Normal size, increased cellularity	Slightly enlarged, increased cellularity	2,160 Gm., anatomically appeared to be leukemia	240 and 220 Gm., anatomically appeared to be leukemia	Myeloid reaction in pericardial fatty tissue	Aleukemic leukemia (myeloblastic)
5	Red, hyperplastic, anaplastic	Normal size, hematopoietic	Slightly enlarged, hematopoietic	Negative	Not enlarged, leukemoid aggregations	Fatty infiltration of viscera	Aleukemic leukemia (myeloblastic)
6	Red, hyperplastic (erythroblastic)	Slightly enlarged, nucleated red cells, fibrosis	Slightly enlarged, nucleated red cells, fibrosis	Fibrosis, erythroblasts	Nucleated red cells, especially in pelvis	Fibrosis and erythroblasts in pancreas	Aleukemic erythroblastosis
7	Grayish red, hyperplastic, anaplastic	Normal size, slightly hematopoietic	Slightly enlarged, slightly hematopoietic	Portal leukemoid aggregations	Leukemoid cellular aggregations	Primitive cells in pancreas	Sepsis, with leukemoid changes
8	Autopsy not done. Developed blood picture typical of myelogenous leukemia. Surgically removed spleen showed hematopoietic activity.						

Following the operation, there was a continuous mild afternoon fever, in spite of which the patient eventually went home and got along fairly well for a time. The blood picture was observed from time to time during the five months that followed. There was not any change except for a slight temporary improvement in the red count.

Two and one-half years after the operation, the patient returned to the hospital. The afternoon fever was still present. The red cell count was 2,010,000, and the white cell count 180,000, with 83 per cent myelocytes. With radiation the white cell count fell to 8,000, but the patient lived only one month longer. Necropsy was not done.

COMMENT

Aleukemic Leukemia.—The five cases described and classified here as aleukemic leukemia showed great diversity from the clinical point of view. They had in common, however, the occurrence of an unexplained severe progressive anemia.

Pathologically, they showed much similarity to one another, the outstanding features being hyperplasia and marked anaplasia of the bone-marrow, with leukemia-like cellular aggregations of various magnitudes in the various organs. The cells in the visceral aggregations always corresponded closely to those in the marrow.

The anemia in cases of typical leukemia is usually considered to be secondary to leukemic "infiltration" of the bone marrow. On the other hand, Helley²⁰ and others believed that changes anatomically resembling those of leukemia may develop in association with certain types of severe anemia. The older term leukanemia, implying as it did an idiopathic anemia with leukemoid manifestations, is, after all, perhaps, the best name that has been proposed for many of these conditions. Sternberg⁷ suggested that certain cases, being more closely related to the leukemias (as case 5 of this series), would be more appropriately termed anemo-leukemia.

In view of the probably neoplastic nature of the true leukemias, about which there is almost universal agreement, it would seem important to draw a sharp line between true leukemia and other, nonneoplastic conditions that are morphologically similar. The difficulty of drawing this line definitely is well brought out by the cases presented. It may be said that, from the anatomic point of view, the relation to true leukemia is quite definite in case 5, somewhat doubtful in cases 1 and 2 and still more doubtful in cases 3 and 4.

Concerning the etiology and nosology of aleukemic leukemia, there is a great difference of opinion. Many pathologists refuse to accept the term, denying the existence of the problem. Lazarus²¹ believed that some cases of pernicious anemia and some cases of leukemia, because of certain deviations from the usual picture, are to be labeled with this term. Sternberg²² believed that these conditions have much in common with the so-called acute leukemias, which he regarded as entirely different from true (chronic) leukemia, considering them to be severe generalized infections with a peculiar reaction on the part of the hematopoietic system. Naegeli,²³ similarly, believed that most cases of aleukemic leukemia are primarily severe anemias of infectious origin.

20. Helley, K. in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 2, p. 1035.

21. Lazarus, cited by Sternberg, footnote 7, p. 56.

22. Sternberg, footnote 7, p. 57.

23. Naegeli, cited by Sternberg, footnote 7, p. 57.

The explanation of certain of the cases of so-called aleukemic leukemia as being caused by infections is to a certain extent supported by several facts brought out in the series of cases described here. In the first place, the clinical pictures, particularly, in cases 1 and 3, were certainly suggestive of infection. The failure to obtain a positive blood culture does not by any means rule out this possibility. The finding of bacteria in the lesions of the kidney in case 5 and in the blood vessels in case 4 lends some support to this conception. Finally, the similarity of the anatomic changes in case 7 (prolonged bacterial intoxication with terminal streptococcus septicemia) to the changes in the cases classified as aleukemic leukemia, strongly suggests that the etiologic factors may be fundamentally similar.

The possibly close relation of some of these conditions to pernicious anemia is strongly suggested by cases 2 and 3. In these cases, the anemia was definitely of the "pernicious" type. In both cases, the general state of nutrition was well maintained. If the bone marrow in these cases is compared with that in pernicious anemia, the principal difference seems to be that in cases 2 and 3 early undifferentiated elements are present to the almost complete exclusion of differentiated elements. Peabody,²⁴ studying the marrow during life from cases of pernicious anemia, showed that relapses are characterized by an increase in the number of primitive cells (megaloblasts), while during remissions the more differentiated cells (erythroblasts) make their appearance. It seems not improbable that, in cases of pernicious anemia running an acute course without remissions, extreme anaplasia of the bone marrow may develop, giving a picture similar to that in cases 2 and 3.

The position of many of these conditions apparently intermediate between pernicious anemia and leukemia has led to the belief that these two conditions may be etiologically in close relationship, their differences being due to variations in the chemical nature and the concentration of the toxic factor or to the individual predisposition. Such a hypothesis was advanced by Ellerman,¹² who, by inoculation of the virus of fowl leukosis in hens, was able to produce a variety of conditions varying from one resembling pernicious anemia through "aleukemic" leukemia to true leukemia. Once established in an individual fowl the type of condition produced always remained constant.

The hematologic classification of these five cases offers great difficulty. Cases 1 and 2 are regarded as definitely of the myelogenous type; for while the majority of the cells in the bone marrow and the other organs were early and undifferentiated in appearance, there was in both cases a plentiful sprinkling of definite myelocytes.

24. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, *Am. J. Path.* 3:179, 1927.

Cases 3, 4 and 5, because of the absence of definite myeloid characteristics, were at first regarded as possibly of lymphoid origin. Generalized enlargement of the lymph nodes and hyperplasia of the lymph follicles in the lymph nodes and in the spleen were not striking in any of these cases. It is unfortunate that the blood smears made during life were discarded, and that attempts to apply various modifications of the oxidase stain to old formaldehyde-fixed material were not successful. Opinions differ greatly, however, as to the value of the oxidase method in such cases. It seems fairly well established that there is a completely nongranular precursor of the myelocyte, which strikingly resembles the various cells of the lymphocytic series. Several German workers (among them Schilling²⁵) stated that these cells often give a positive oxidase reaction in spite of their nongranular character, while Jolly²⁶ and others found these cells oxidase-negative.

If one believes with Maximow²⁷ and others that the lymphocyte is an undifferentiated cell identical with the hematocytoblast or earliest blood cell, the separation of undifferentiated cell leukemias into lymphatic and myelogenous types becomes unimportant.

Ellerman,¹² working with fowl leukosis, described an "intravascular lymphoid leukosis" in which the type cell markedly resembled a lymphocyte but was regarded by him as the progenitor of the erythroblast. This condition, which was characterized by severe anemia, he designated "erythroleucosis." It must be admitted that there is not a positive method of distinguishing in fixed tissues between the myeloblast and the early megaloblast. The severe anemia in the cases reported here and the almost complete absence of adult granulocytes in the marrow suggest that the erythropoietic tissue rather than the leukopoietic tissue is primarily involved. An attempt was made to substantiate this conception by measuring the angles of mitosis of the primitive cells, Ellerman and Petri²⁸ believing that the angle for the myeloblast is 60 degrees, and the angle for the erythrogonium is 20. Although mitoses were frequent in all the marrows, spindles were rarely found and the material appeared to be unsuitable for a study of this nature.

Careful work led Cunningham, Sabin and Doan²⁹ to the belief that endothelium gives rise to megaloblasts and the red cell series, while the

25. Schilling, V.: *Das Blutbild*, ed. 2, Jena, Gustav Fischer, 1922, pp. 70 and 119.

26. Jolly, J.: *Traité technique d'hématologie, morphologie, histogenèse, histophysiologie, histopathologie*, Paris, A. Maloine et fils, 1923, p. 370.

27. Maximow, A.: *Morphology of Mesenchymal Reactions*, Arch. Path. **4**: 557 (Oct.) 1927.

28. Petri, S.: *Histologische Untersuchung eines Falles von myeloischer leukämie mit messung der Mitosenwinkel*, Folia Haemat. Arch. **32**:103, 1926.

29. Cunningham, R.; Sabin, F., and Doan, C.: *The Development of Leukocytes, Lymphocytes, and Monocytes from a Specific Stem Cell in Adult Tissue*, Contrib. Embryol. 82, Carnegie Inst., Washington **16**:227, 1925.

reticular cell gives rise to myeloblasts, monoblasts and, at times, lymphoblasts. Other workers,²⁷ however, postulated a common stem cell for both the erythrocytic and the granulocytic series. Even if it is assumed that the red cells normally come from endothelium, it is possible that, under pathologic conditions, reticulum cells also are their ancestors.

In the present state of our knowledge, it must be admitted that instances of atypical leukemia occur in which the type cell cannot be classified as a lymphocyte or an early myeloblast or megaloblast with any degree of certainty, even with the help of the oxidase reaction.

Sternberg²¹ believed that practically all cases of acute leukemia are myelogenous in type, those that have been regarded as of lymphocytic origin being simply cases in which the type cell is primitive and consequently of a lymphoid appearance. The supravital technic of staining offers a possible method of approach to this question.

As has been stated, the essential pathology of the marrow in the cases reported here is the replacement of differentiated elements by primitive cells. In secondary anemias and in leukocytosis one finds this process of anaplasia in a slight degree only, the reversion in cases of erythropoiesis being principally from the adult red cell to the erythroblast, and in cases of leukopoiesis from the adult granulocyte to the late myelocyte. The occurrence of early cells (megaloblasts and myeloblasts) in the marrow in large numbers is generally characteristic of the more severe disorders of the blood (pernicious anemia and myelogenous leukemia).

The anaplasia in the cases reported here is more complete than that found in either pernicious anemia or the true leukemias, and it seems probable that in these cases the majority of the cells in the marrow that have been classified as early myeloblasts or megaloblasts are in reality only slightly more differentiated than the reticular cells or the endothelial cells.

The appearance of the cells composing the visceral aggregations in these cases (especially case 3) strongly supports the belief that the blood cells may, under abnormal conditions, be formed directly from undifferentiated mesenchymal elements, variously known as adventitial cells (Marchand), clasmotocytes (Ranvier), polyblasts (Ziegler) and hemato-histioblasts (Ferrata).

The peculiar gigantic cells that were so numerous in the bone marrow and other organs in cases 1 and 2 deserve special mention. Apparently similar cells have been reported as the outstanding feature in certain rare cases of true leukemia (Schwarz,³⁰ Himbdenberg,³⁰ Barth,³⁰ Koerner³⁰),

30. Schwarz, Himbdenberg, Barth, Koerner; cases summarized by Lubarsch in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 2, p. 658.

and of aleukemic leukemia (Firket and Campos³¹). These cells have been variously regarded as true megakaryocytes (Koerner³⁰) and as hypertrophic early blood-forming cells (Barth³⁰). Jaffe¹⁷ gave the latter interpretation to similar large cells that were present in smaller numbers in his cases of "aleukemic myelosis."

The article by Firket and Campos³¹ is of particular interest. These workers reported a case in which gigantic cells were the outstanding feature of the visceral changes. The blood picture was aleukemic and the bone marrow aplastic (fatty). Previous exposure to benzol was a possible etiologic factor. By the intravenous injection of saponin in rabbits, these workers were able to produce a generalized myeloid metaplasia, in which large cells (regarded as megakaryocytes) were the outstanding feature. Their interpretation is that saponin has a particularly destructive action on the blood platelets, leading to regenerative hyperplasia of the megakaryocytes. They minimize the resemblance of the experimentally produced lesion to that in the reported case, chiefly because the bone marrow in the latter was fatty. The changes that they produced by the injection of saponin certainly resemble markedly, from an anatomic standpoint, the changes present in the organs of the patient in case 1 of this series. It would seem worth while to carry out further work along these lines, using various toxic and hemolytic substances, including bacterial toxins.

Erythroblastosis.—The justification for applying this term to case 6 is that the latter appears to be a case of an atypical leukemoid condition in which the bone marrow is hyperplastic, differentiation being apparently arrested at the stage of the erythroblast. The presence of large numbers of nucleated red cells in the mesenchymal tissue of nearly all the organs seems best explained as a myeloid, or rather erythroblastic metaplasia.

The term fetal erythroblastosis has been applied (Eichelbaum³²) to a condition occurring in newly born infants, practically always in association with congenital edema. The anatomic changes in such cases seem to be merely an exaggeration of the extramedullary hematopoietic activity frequently noticed at birth (especially in association with congenital syphilis). The occurrence of a similar condition in older children or adults has not, as far as can be learned, been previously reported.

Erythroblastoma (localized tumor-like masses of erythroblastic tissue, usually in the bone marrow) is a rare but well recognized condition, and similar tumor-like masses have been reported in the suprarenal

31. Firket, J., and Campos, E.: Generalized Megalokaryocyte Reactions to Saponin Poisoning, *Bull. Johns Hopkins Hosp.* **33**:271, 1922.

32. Eichelbaum: Hydrops congenitus, *Arch. f. Gynäk.* **119**:149, 1923.

gland (Mieremet³³). In a case reported recently (Warren³⁴), diffuse tumor-like masses were present in the pelvises of both kidneys, while the liver and the other organs showed striking leukemoid changes. In a case observed at the Peter Bent Brigham Hospital (not yet reported) in which there was marked splenomegaly, a pyelogram revealed the presence of a renal or retroperitoneal tumor mass in the region of the right kidney. An excised cervical node showed extreme hematopoietic activity with many large islands of nucleated red cells and marked fibrosis and distortion of the architecture. This patient died. A necropsy was not obtained.

These observations may indicate that in the erythroblastic tissue, as well as in the leukoblastic and lymphoblastic tissue, intermediate types of disease may be found ranging from localized neoplasm to leukemia-like conditions. From this point of view, it seems proper to classify case 6 as aleukemic erythroblastosis (corresponding to aleukemic myelosis and lymphadenosis).

Leukemoid Conditions Secondary to Infection.—The blood in acute infections may undergo extraordinary changes in its composition, from the leukopenia of typhoid fever and the lymphocytosis of certain acute infections to a polymorphonuclear leukocytosis with a white count exceeding 200,000. These changes, of course, represent the normal functioning of the defense mechanism against bacterial invasion.

The alteration produced in the blood-forming tissues in these infections is a simple hyperplasia, differentiation being chiefly in the direction of that type of blood cell that is being most actively destroyed. On recovery from the infection there is a rapid return to the normal condition in the bone marrow. The hyperplasia is, as a rule, confined to the bone marrow, although in certain cases of chronic infection a slight myeloid activity may be found in the spleen.

In certain infectious processes, notably infectious mononucleosis¹⁵ and agranulocytic angina,¹⁶ more profound alterations are to be found in the circulating blood. These two conditions bear a certain resemblance to each other. Necrotic lesions of the mouth and the tonsils are common to both. In agranulocytosis there is leukopenia, with a marked decrease in the circulating granulocytes, while in mononucleosis there is a variable lymphocytic (?) leukocytosis. Agranulocytosis is usually fatal, while mononucleosis is never fatal. In certain cases described in the literature as agranulocytosis (Krumbhaar,⁸ Moore and Wieder³⁵)

33. Mieremet, C. W. G.: Ein aus dem verschiedenen Elementen des Knochenmarks bestehender Tumor in der Nebenniere, *Centralbl. f. allg. Path. u. path. Anat.* **30**:403, 1919.

34. Warren, S.: Malignant Tumor Simulating Bone Marrow, *Am. J. Path.* **4**:51, 1928.

35. Moore, J. A., and Wieder, H. S.: Agranulocytic Angina; Report of a Case with Two Attacks, *J. A. M. A.* **85**:512 (Aug. 15) 1925.

there was only a mild leukopenia, and these cases frequently recover. Such cases as these greatly resemble infectious mononucleosis, the only difference being that the abnormal cells have been regarded as myeloblasts instead of lymphocytes or monocytes. Thus, the mild cases of agranulocytosis resemble infectious mononucleosis, while the fatal cases are remarkably similar to the so-called acute leukemia.

Reports of postmortem examinations in cases of infectious mononucleosis are not to be found in the literature (because of its invariably favorable termination), so that we are left in the dark regarding the occurrence of leukemia-like visceral changes in this condition. Excised lymph nodes¹⁵ usually show hyperplasia, an increased cellularity (atypical mononuclear cells being numerous) and a few eosinophils—in short, little more than one might see in a lymph node draining an area of sepsis.

Postmortem examinations in cases of agranulocytosis are also rare. Sternberg¹¹ reported a case in which stomatitis was present, with marked leukopenia and a relative lymphocytosis. This patient died with streptococcus septicemia. At autopsy, the bone marrow was found cellular, being composed chiefly of "round" cells that were oxidase-negative. The kidneys and the liver showed moderate cellular aggregations, which, as far as can be learned from the description, were of about the same order of magnitude as those seen in case 7 of this series. Sternberg regarded this case as one of acute leukemia.

Krumbhaar⁸ also reported a case of severe gastrocolitis in which streptococcus septicemia developed shortly before death. Two days before death there was a polymorphonuclear leukocytosis. On the day before death, the white count was 69,000, with 55 per cent atypical mononuclear cells that were apparently myeloblasts. At autopsy, leukemia-like collections of similar cells in the various organs were sufficiently striking to raise seriously the question whether the condition might be acute leukemia. He was inclined to regard it, however, as an abnormal response of the hematopoietic system to infection. It is to be noted that this is Sternberg's definition of acute leukemia.

Nyiri³⁶ reported a case in which there was fever, stomatitis and a white count of 7,700, with 34.2 per cent of "unripe" myeloid elements. A hemolytic staphylococcus was recovered from the blood stream, but the patient made a complete recovery.

The similarity of the picture in the kidneys in cases 5 and 7 to that of the so-called acute nonsuppurative interstitial nephritis, is perhaps worth mentioning. In this latter condition, which is observed chiefly in children that have died of diphtheria or scarlet fever, the kidney may be

36. Nyiri: *Wien. klin. Wchnschr.* **37**:907, 1924.

quadrupled in weight (Councilman³⁷), with tremendous accumulations of cells between the tubules and around the glomeruli and blood vessels. These cells appear to be partly of the lymphoid series, partly plasma cells and partly atypical mononuclear cells, with a variable but often insignificant number of polymorphonuclear leukocytes. The small amount of degenerative change has been regarded as secondary to the cellular aggregations, rather than as the cause of them. Accumulations of cells similar to but less striking than those found in the kidneys have been described as occurring in the heart, bone marrow, spleen and liver in these cases. The term acute lymphomatous nephritis has been applied to the condition.

The origin of these cells has been in dispute. Mitotic figures are frequent among them, and they multiply largely in situ. Various workers have suggested their possible local origin from undifferentiated mesenchymal elements. Von Möllendorff³⁸ and his followers recently became convinced that the various cells that appear in the tissues in response to inflammation (including the polymorphonuclear leukocytes) have a local origin. Although the evidence that these workers presented by no means overthrows the well established belief that the origin of the polymorphonuclears in acute inflammation is in the bone marrow, it is possible that the local metaplastic origin of blood cells may become of importance under certain conditions.

The anatomic observations in these cases of nonsuppurative interstitial nephritis do not differ materially from those of many cases of so-called aleukemic leukemia, and if one were not aware of the underlying cause (acute infection) there would be serious danger of confusing the two conditions.

Leukemoid Conditions Secondary to Other Destructive Lesions of the Blood and the Hematopoietic System.—There is some evidence that true leukemia may at times develop on the basis of a preexisting hyperplasia of the hematopoietic system. Case 8 of this series, in which an unknown type of "splenic anemia" eventually presented itself as myelogenous leukemia, is almost duplicated by a case in the series reported by Krumbhaar.⁸ Cases have been reported in which true myelogenous leukemia was superimposed on a picture of prolonged severe anemia of malarial origin (Decastello³⁹). The frequent occurrence of leukemoid blood pictures and the occasional development of

37. Councilman, W. T.: Acute Interstitial Nephritis, *J. Exper. Med.* **3**:393, 1898.

38. Von Möllendorff, W.: Die örtliche Zellbildung in Gefasswänden und in Bindegewebe, München. med. Wchnschr. **73**:135, 1927.

39. Decastello: Acute Leukaemie und Sepsis, *Wien. Arch. f. inn. Med.* **11**: 217, 1925.

true myelogenous leukemia in cases of erythremia was stressed by Minot⁴⁰ and others.

In pernicious anemia the regenerative hyperplasia usually stays within normal bounds, but myeloid changes may be found in the spleen, liver and lymph nodes, the frequency being in the order mentioned. Myelogenous leukemia has been reported as developing in cases of pernicious anemia, but Jaffé¹⁷ suggested that such cases may initially have been "aleukemic myelosis."

Myeloid metaplasia may occur in the liver and the spleen in cases in which the bone marrow has been destroyed by metastatic carcinoma (McCallum⁴¹), and the same picture is seen in certain cases of osteosclerotic anemia. Sternberg¹¹ believed that these changes are in most cases secondary to marrow fibrosis from various causes, although in rare cases the fibrosis may be secondary to leukemia.

On the whole, the development of leukemoid conditions and true leukemia on the basis of regenerative hyperplasia of the hematopoietic system appears to be about as frequent as the development of benign and malignant neoplasms following functional or regenerative hyperplasia of epithelial tissues.

CONCLUSIONS

Five cases of "aleukemic leukemia" are reported which show a general pathologic similarity but a striking clinical diversity. Anatomically, the outstanding features of these cases were hyperplasia and extreme anaplasia of the bone marrow, and the presence in the viscera of foci of early myeloid cells, which probably originated largely by metaplasia from undifferentiated mesenchymal elements. These anatomic changes are not pathognomonic of "aleukemic leukemia," since a similar picture may be produced by prolonged sepsis (either because of destruction of the blood or through toxic action on the marrow).

In such extremely anaplastic marrow, the majority of the cells show so little evidence of differentiation that it is not always possible to determine whether the hyperplasia is primarily leukoblastic, erythroblastic or lymphoblastic.

Clinically, the only constant fact in these cases was severe anemia. The clinical pictures and pathologic changes lend considerable support to the view that many of these conditions are primarily severe anemias of infectious or toxic origin with atypical regenerative hyperplasia of the hematopoietic system. This point of view is further strengthened by case 7, in which similar leukemia-like visceral aggregations developed, apparently secondary to a severe anemia accompanying prolonged sepsis.

40. Minot, J. R., and Buckman, T. E.: Erythremia, *Am. J. M. Sc.* **166**:469, 1923.

41. McCallum, W. G.: *Textbook of Pathology*, ed. 2, Philadelphia, W. B. Saunders Company, 1920.

A similarity is pointed out between certain cases of subleukemic visceral myeloid metaplasia and the so-called "acute nonsuppurative interstitial nephritis."

One case of acute aleukemic erythroblastosis is reported that appears to be unique in the literature, and one case in which the picture of myelogenous leukemia was superimposed on that of a "splenic anemia" of several years' duration.

Some evidence is presented for the belief that leukemoid conditions and even true leukemia may at times develop on the basis of a pre-existing nonspecific hyperplasia of the blood-forming tissue.

EXPLANATION OF FIGURE 12

Fig. 12.—The sections *A* to *G* present representative cells from the bone marrow of cases 1 to 7. The cells shown for each case are of the type that greatly predominate (from 90 to 98 per cent). The drawings were all made at a constant magnification.

A (case 1): Eosin-methylene blue stain. Hyperplastic, primitive, blood-forming cells, frequently multinucleated. The relation of the cells to the intercellular substance may be noted.

B (case 2): Eosin-methylene blue stain. The cell in the upper left corner is probably an early megaloblast, while the other cells correspond to early myeloblasts or "primitive free cells."

C (case 3): Hematoxylin eosin stain. The indentation and lobulation of the nuclei may be noted. These cells are probably derived from the reticulum cells, one of which is shown in the center of the figure.

D (case 4): Eosin-methylene blue stain. The two large cells are probably early megaloblasts, the others early myeloblasts.

E (case 5): Eosin-methylene blue stain. The nuclei are small, hyperchromatic and frequently lobulated. The large cell is probably a hypertrophic reticulum cell.

F (case 6): Hematoxylin eosin stain. Erythroblasts are shown, many of which have lobulated and shriveled nuclei. Two megaloblasts are present.

G (case 7): Giemsa stain. Although stained somewhat differently, these cells are comparable to those in the marrow of cases 2 and 4 (*B* and *D*).

H (case 6): Erythroblastic metaplasia of loose areolar tissue of the mesentery, about 2 mm. distant from the capsule of a small lymph node. Eosin-methylene blue stain. Most of the cells are erythroblasts, but a few reticulum cells and intermediate stages are shown. It may be noted that the erythroblasts are extravascular. In the right lower quadrant is a large erythroblast (in mitosis?) and to the right of this cell is a basophil cell (megaloblast?) which is beginning to accumulate hemoglobin.

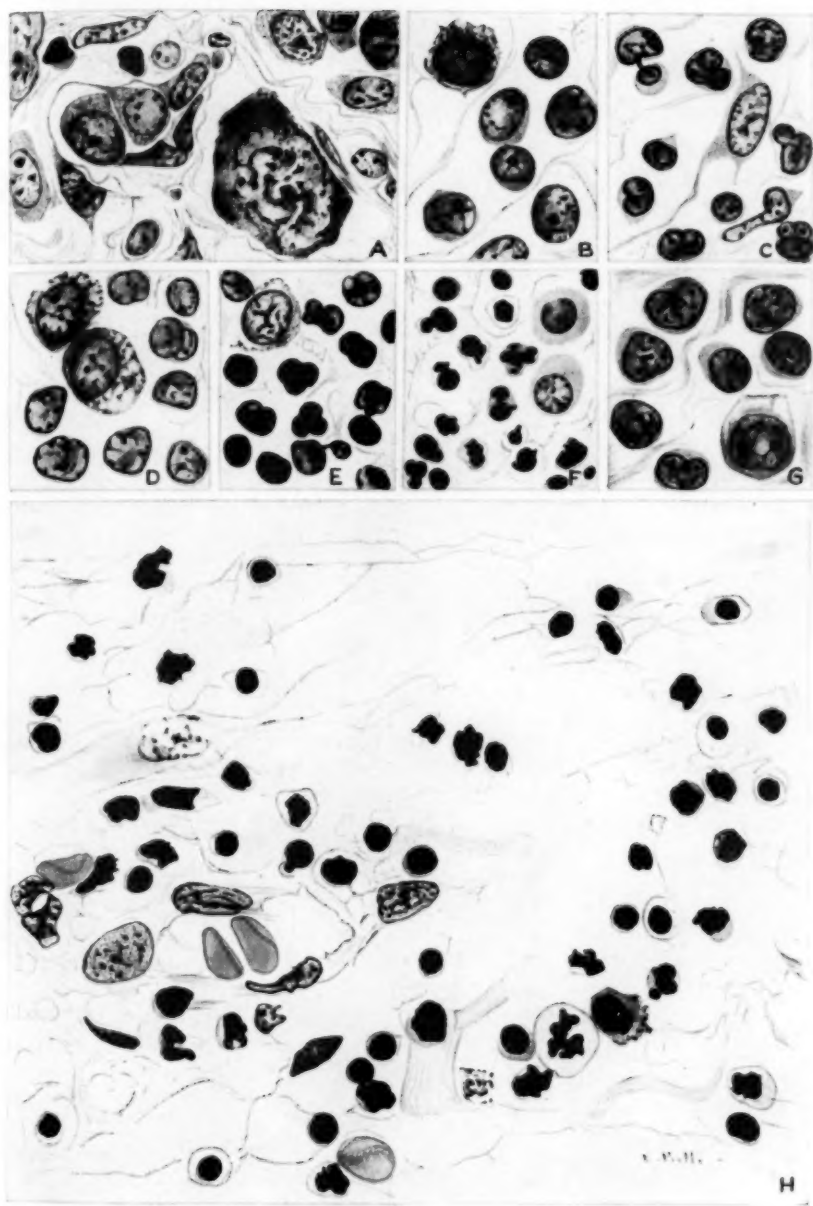


Figure 12

CERTAIN EFFECTS OCCASIONED IN DOGS BY DIPHThERIA TOXIN

I. A REPORT OF THE VISCERAL LESIONS *

HAROLD J. STEWART, M.D.

NEW YORK

In the course of experiments in another connection, I had occasion to inject diphtheria toxin intravenously into the circulation of normal dogs. Some of the results were so striking that I have decided to add them to the literature dealing with the pathologic changes resulting from the injection of diphtheria toxin. The experiments are of interest both to the clinician and to the pathologist. In this paper, I present certain effects of the injection of diphtheria toxin on the heart observed while the animals were living, as well as the gross and microscopic observations at autopsy. In a second paper, I shall describe the changes that took place in the size of the heart, and give other data connected with the occurrence of these changes.

MATERIAL AND METHOD

Mongrel dogs of widely differing weights were used. The diphtheria toxin was obtained from the New York City Board of Health. It was injected intravenously in the ear. The minimal lethal dose for guinea-pigs was 0.00125 cc. As one lot of the toxin was sufficient for the series of experiments, its strength was approximately constant. The toxin was diluted with sterile physiologic sodium chloride solution. Not finding any mention in the literature of the minimal lethal dose of diphtheria toxin for dogs, I roughly calculated a dose based on the ratio of the weight of the dog to the weight of the guinea-pig. Since I did not wish the animals to die too soon after the injection, in the first experiments I injected a dose per kilogram of body weight that I estimated would prove fatal within several days. In later experiments, I tested within narrow limits the amount of toxin per kilogram of body weight that would be followed by a fatal outcome.

During the course of these experiments, roentgenograms of the heart and electrocardiograms were taken almost daily. Records of the body weight were made at the same time. In some cases, the urine was tested for albumin and examined microscopically. Because of jaundice, the urine and the blood plasma were examined for bile pigments. At autopsy, the material was examined in the gross, and sections of the organs were taken for microscopic study.

The hearts, at autopsy, after the removal of blood clots, were fixed whole in 10 per cent formaldehyde solution. The method of fixation and preparation for section was that described by Lewis.¹ The separation of the fixed heart into the

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* From the Hospital of the Rockefeller Institute for Medical Research.

1. Lewis, T.: Observations upon Ventricular Hypertrophy with Especial Reference to Preponderance of One or the Other Chamber, *Heart* 5:367, 1913-1914.

right and the left ventricles was carried out according to a method devised by Herrmann and Wilson.² These were weighed, and the ratio of the weight of the right ventricle to that of the left ventricle (called here the L/R ratio) and the ratio of the combined weights of both ventricles to the body weight ($\frac{L+R}{B\ W}$) were calculated.

The dogs were divided into groups 1 and 2, group 2 being subdivided into groups A, B and C,³ the basis of the division being the amount of toxin injected per kilogram of body weight, decreasing amounts being given in the succeeding groups.

OBSERVATIONS FOLLOWING THE INJECTIONS

Course and Autopsy.—GROUP 1.—The four dogs in this group (nos. 81, 82, 83 and 84 of table 1) received approximately the same amount each of toxin per kilogram of body weight, given in two doses varying from 0.00161 to 0.00232 cc. for the first dose, and from 0.00105 to 0.00168 cc. for the second dose, the total being from 0.00327 to 0.00337 cc. The interval of time between the two doses varied from two to four days. Following the injections, the dogs became ill, ate little and lost weight; they died from three to five days after the first injection. Three dogs (nos. 81, 82 and 83) developed marked jaundice of the skin and the sclerae, which was at a maximal intensity at the time of death. At autopsy, the skin and the subcutaneous tissues were stained an intense yellow, as were also the membrane lining the pleural cavity, the pericardial fat and the large blood vessels. There were ecchymoses in the subcutaneous tissues, along the intercostal blood vessels, in the pericardial fat, sometimes in the visceral pericardium, in the kidney capsule and often in the cortex of the kidney. The lungs from two animals showed large areas of consolidation and, in one instance, marked edema.

GROUP 2 A.—Nine dogs (nos. 85, 86, 87, 97, 99, 102, 103, 104 and 105 of table 2) received each, in a single injection, 0.00168 cc. of toxin per kilogram of body weight. These dogs showed the same objective symptoms as the animals in group 1, and died from two and a half to five days after the injection. Eight developed marked jaundice of the skin, which in some of the animals, appeared only shortly before death. The gross observations at autopsy did not differ from those made in the dogs belonging to group 1. Dog 104 lived for two and a half days following the injection of the toxin; it did not show any jaundice, but ecchymoses were present at autopsy. Dog 85 moved during the injection, so that about half of the dose of toxin was given subcutaneously. This dog lived for eight days after the injection, but showed the same clinical course as the other dogs of this group, including jaundice and gross lesions at autopsy.

GROUP 2 B.—Six dogs (nos. 107, 108, 109, 110, 111 and 112 of table 3) were each given, in one injection, 0.00135 cc. of toxin per kilogram of body weight. These did not become so acutely ill as the animals receiving the larger doses; they lost weight and died from four to nineteen days after the injection of toxin. Paralysis of the limbs were occasionally seen in these animals. Only one dog (no. 108) developed jaundice and showed ecchymoses at autopsy.

GROUP 2 C.—Five dogs (nos. 88, 89, 90, 101 and 106 of table 4) received each, in one injection, 0.001 cc. of toxin per kilogram of body weight. Four did not

2. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy: A Comparison of Electrocardiographic and Postmortem Observations, *Heart* 9:91, 1922.

3. Group 2 is subdivided in this manner in order that this paper may agree, in arrangement of the material, with the second paper of this series.

TABLE 1.—Summary of the Clinical and Postmortem Observations in the Dogs of Group 1

Dog*	Weight, Kg.	Toxin per Kilogram of Body Weight		Day of Death After Injection of Toxin	Jaun- dice	Ecchy- moses at Au- topsy	Summary of Microscopic Observations					Electro- cardio- gram R ₂ and R ₃ decreased	L/R Ratio 1.38	L + R B W		Ratio Initial Body Weight at Autopsy 0.00483 0.00572
		First Dose, Cc.	Second Dose, Cc.				Heart	Lungs	Liver	Kidneys	Spleen					
81 ♀	10.75	0.00232	0.00105 0.00637	2	3d	+	One small area of leukocytic infiltration	Broncho- pneu- monia; small abscesses	Central ne- crosis; phagocy- tosis by Kupfer cells; nests of round cells and cells resem- bling nu- cleated red cells	Necrosis of tubu- lar epi- thelium; nuclei not seen in these areas	Negative	R ₂ and R ₃ decreased	1.25	0.00608	0.00574	
83 ♂	7.95	0.00166	0.00106 0.00632	2	3d	+	A: a few red cells; B: a few red cells; C: small areas of round cell infiltra- tion; D: normal	Pneu- monia	Central necrosis; bile throm- bi; phago- cytosis; clumps of round cells and cells resembling nucleated red cells	0	No sec- tion	No change	1.21	0.00606	0.00702	
84 ♂	8.90	0.00166	0.00106 0.00536	2	3d	0	Small area in which muscle fibers are replaced by fibrous tissue	Conges- tion	Central necrosis; necrotic areas with red cells; clumps of round cells and cells resembling nucleated red cells	Necrosis of tubules; red cells between tubules; collections of round cells and cells resembling nucleated red cells (?)	No sec- tion	R ₂ and R ₃ decreased	1.24	0.00472	0.00535	

* In this column, ♀ indicates female; ♂, male.

† The letters refer to the location in the heart from which the section was taken: A, from the septal wall near the base; B, from the posterior wall of the left ventricle near the base; C, from the posterior wall near the apex; D, from the right ventricle near the base.

TABLE 2.—Summary of the Clinical and Postmortem Observations in the Dogs of Group 2 A

Dog	Sex	Weight, Kg.	Toxin per Kg., Cc.	No. Days Animal Lived After Injection of Toxin	Jaundice	Bile Pigment in Urine	Bile Pigment in Plasma	Urine	Echymoses at Autopsy	Summary of Microscopic Observations				Electrocardiogram	L/R Ratio	L + R Ratio	
										Heart	Lungs	Liver	Kidneys	Spleen		Initial Body Weight	Body Weight at Autopsy
85	♂	7.00	0.00108	8	+	+	+	White cells +	0	Red cells scattered between muscle cells	Congestion; one necrotic area	Central necrosis, which is being replaced by regenerating liver cells	Areas in which tubular epithelium is flattened and tubules filled with casts; small abscesses in cortex; increase in interstitial tissue; glomeruli fibrotic and large	1.39	0.00585	0.00762
86	♀	9.77	0.00108	3	+	+	Granular appearance of muscle cells	Congestion	Central necrosis; collection in necrotic areas; phagocytosis; round cell infiltration, cells resembling normoblasts	Infarct; areas of necrosis of tubules; old scar on surface; collections of round cells resembling normoblasts	1.15	0.00532	0.00615
87	♀	10.10	0.00108	3	+	+	Negative	Edema	Central necrosis; phagocytosis; congestion in necrotic areas; collections of round cells resembling nucleated red cells	Small hemorrhagic areas	1.07	0.00497	0.00595
97	♀	10.20	0.00108	3	+	0	0	Red cells ++; white cells +	+	Large bacilli	Congestion	Central necrosis; no traces of nuclei in the section; large bacilli	Fresh infarct	Spaces engorged with blood	1.36	0.00442	0.00408

99 ♂	14.00	0.00108	6	+	+	0	0	0	White cells +; occasional granular casts	Negative	Congestion; edema	Central necrosis; engorged with red cells; cells resembling nucleated red cells	Large area of necrosis including tubules and glomeruli; small areas of round cell infiltration; normoblasts	R ₂ and R ₃ decreased	1.26	0.00656	0.00715
102 ♂	14.00	0.00108	4	+	+	+	+	+	Trace of albumin; epithelial cells and white cells in casts	Negative	Congestion	Central necrosis; red cells in necrotic areas; cells resembling nucleated red cells	A few scattered necrotic tubules; tubular epithelium swollen; epithelial cell casts	Congestion	R ₂ and R ₃ decreased	1.12	0.00495	0.00563
103 ♂	11.20	0.00108	4	+	+	+	+	+	Marked traces of albumin; coarse granular casts	Negative	Pneumonia	Central necrosis engorged with red cells; bile thrombi; cells resembling nucleated red cells	Necrosis of tubules; casts	R ₂ and R ₃ decreased	1.19	0.00621	0.00676
104 ♂	9.02	0.00108	2½	0	0	0	0	0	Marked traces of albumin; occasional granular cast	Area of hemorrhage	Congestion; hemorrhage	Marked central necrosis; cells resembling nucleated red cells in collections of normal cells	Areas of round-cell infiltration	R ₂ and R ₃ decreased	1.27	0.00684	0.00719
105 ♂	11.12	0.00108	5	+	+	+	+	+	Trace of albumin	Negative	Congestion; edema	Central necrosis; phagocytosis; collection of round cells; cells resembling nucleated red cells	Interstitial changes; glomeruli replaced by round, polymorphous nuclear and connective tissue cells	R ₂ and R ₃ decreased, then increased	1.31	0.00631	0.00616

* In this column, ♀ indicates female; ♂, male.

TABLE 3.—Summary of the Clinical and Postmortem Observations in the Dogs in Group 2 B

Dog	Sex ^a	Weight, Kg.	Toxin per Kg., Cc.	Number Days Lived After Injection of Toxin	Jaundice	Bile in Urine	Urine	Ecchymoses at Autopsy	Electro- cardiogram	L/R Ratio	L + R BW Ratio	
											Initial Body Weight	Body Weight at Autopsy
107	♂	17.15	0.00135	12	0	No change	1.36	0.00465	0.00621
108	♂	19.15	0.00135	4	+	0	Faint trace of albumin	+	R ₂ and R ₃ decreased	1.37	0.00505	0.00535
109	♂	15.38	0.00135	16	0	R ₂ and R ₃ decreased, then increased	1.45	0.00463	0.00591
110	♂	13.85	0.00135	19	0	R ₂ and R ₃ decreased	1.30	0.00423	0.00522
111	♂	16.45	0.00135	11	0	Epithelial cells +; white cells +	0	R ₂ and R ₃ decreased	1.23	0.00478	0.00562
112	♂	14.70	0.00135	13	0	0	No change	1.34	0.00500	0.00523

^a In this column, ♀ indicates female; ♂, male.

TABLE 4.—Summary of the Clinical and Postmortem Observations in the Dogs in Group 2 C

Dog*	Weight, per Kg., Ce.	Toxin Infection	No. Days Animal Lived	Jaun- dice	Bile in Urine	Plasma	Urine	Echy- moses at Au- topsy	Microscope Observations			Electro- cardiogram	L/R Ratio	L + R BW		Ratio
									Heart	Lungs	Liver	Kidneys		Initial Body Weight	Body Weight at Autopsy	
88 ♂	7.92	0.001	Lived	0	No change
89 ♀	6.70	0.001	Lived	0	No change
91 ♂	11.20	0.001	Lived	0	White cells +++	No change
101 ♀	12.30	0.001	Lived	0	0	0	Few leu- kocytes, epithelial cells; faint trace of albumin	Ra and R _s decreased, then increased
103 ♀	11.57	0.001	22	0	0	+	Faint trace of albumin white cells +++; oc- casional hyaline cast	0	Cells re- sembling fibro- blasts	Conges- tion; edema	Central cells stain pale, but definite necrosis not present; phagocy- tosis; small areas of fibro- blastic tissue in central area, though necrotic area had healed	Blood vessels engorged; bile stained casts	Heart block 3 days before death	0.00468	0.00792	0.00792

* In this column, ♀ indicates female; ♂, male.

become ill, and did not show any clinical evidence of intoxication, except a loss of weight, which was as great as that in the dogs receiving the larger doses. These four dogs were still living and well twelve months after receiving the toxin. One dog (no. 106) did not fall ill immediately after the injection, although ten days later it did, lost weight rapidly and died on the twenty-second day after the injection. At autopsy, jaundice and ecchymoses were not seen.

Urine.—Examinations of the urine were made in the cases of several dogs. The specimens showed from faint to marked traces of albumin. Microscopically, a few leukocytes and epithelial cells were found following the injection of 0.001 cc. of toxin (dog 101), and red cells, white cells and coarse granular and hyaline casts following the larger doses (as shown in tables 1 to 4).

The urines of ten dogs were tested for bile by Rosenbach's method (nos. 85, 97, 99, 101, 102, 103, 104, 105, 106 and 108). Of these ten dogs four (nos. 85, 102, 103 and 105 of tables 1 to 4) had bile in the urine, and the corresponding blood plasma of three showed the presence of bile pigments. In two dogs showing jaundice clinically (nos. 97 and 99), neither the blood plasma nor the urine gave positive results in tests for bile.

Effect on the Heart.—In the electrocardiograms of thirteen of nineteen dogs that had received each 0.00135 cc. or more of toxin per kilogram of body weight there was a progressive decrease in the amplitude of waves R_2 and R_3 (dogs 81, 82, 84, 86, 87, 97, 99, 102, 103, 104, 108, 110 and 111 of tables 1 to 4). The electrocardiograms of dog 86, in addition to showing the decrease in R_2 and R_3 waves (fig. 1 *A* and 1 *B*), also showed the development of S_2 and S_3 waves (fig. 1 *C*). Changes were not apparent in the heart rate, the conduction time, the QRS interval and the T-wave. The records of dog 106 showed complete heart block for three days before death. This animal received only 0.001 cc. of toxin per kilogram of body weight.

The L/R ratios of the hearts of the dogs into which diphtheria toxin had been injected, varied between 1.07 and 1.45 (tables 1 to 4). In all except dog 109, the ratio was less than the average L/R ratio of normal dogs (fig. 2); that is to say, the left ventricle apparently lost more weight than did the right ventricle. But taken in conjunction with the ratio of the combined weights of the $\frac{L+R}{B+W}$ ratios, the change in the ratio is probably to be ascribed to a loss of weight rather than to an actual right ventricular hypertrophy or a left ventricular atrophy in the short time of a few days.

The ratio of the combined ventricular weight (L + R) to the body weight varied between 0.00468 and 0.00874 (as shown in tables 1 to 4). Twelve of the ratios were below the average for normal dogs and eight above the average (fig. 3). If the weight of the animal just before the injection of diphtheria toxin was used in calculating the $\frac{L+R}{B+W}$ ratio, this ratio in sixteen animals was below the average and in only four instances was above the average.

Microscopic Examination.—Heart: In dog 83, microscopic sections were made from the septal wall of the heart near the base (*A*), from the posterior wall of the left ventricle near the base (*B*), from the posterior wall near the apex (*C*) and from the right ventricle near the base (*D*), as shown in table 1. In the other hearts, sections were taken from the posterior wall of the left ventricle. In none of these sections was there a striking change in the histologic appearance of the muscle fibers and the interstitial tissue. A section of one heart showed isolated red cells scattered between the muscle fibers, and sections of two other hearts showed the transverse striations not clearly marked.

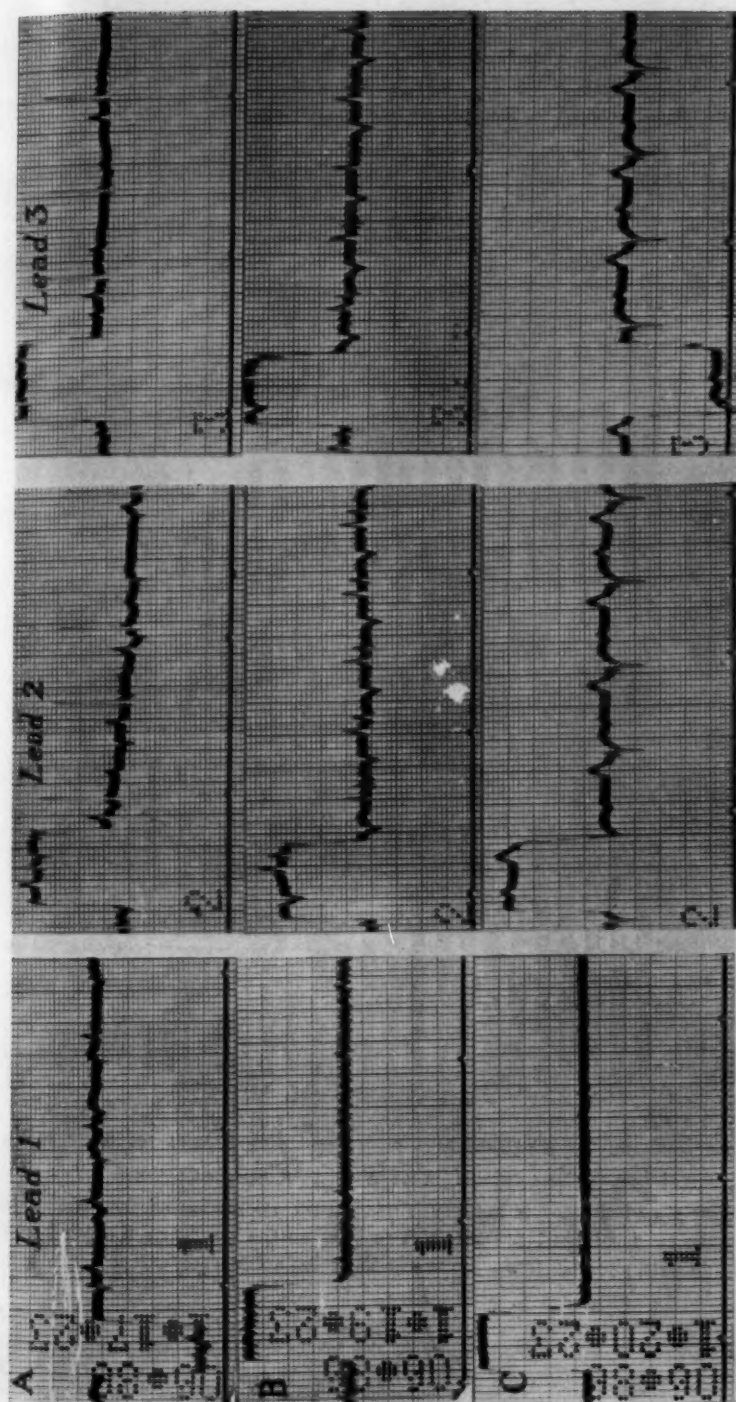


Fig. 1.—Electrocardiograms of dog 86. *A*, taken on Jan. 17, 1923, before the injection of diphtheria toxin; *B*, taken on Jan. 19, 1923, two days after the injection of 0.00168 cc. of diphtheria toxin per kilogram of body weight; *C*, taken on Jan. 20, 1923. Divisions of the ordinates equal 10^{-4} volts. Divisions of the abscissae equal 0.04 second. Reduction, two-thirds natural size.

Lungs: Sections from the lungs of several dogs showed fresh infarcts. Sections from others disclosed the capillaries engorged with red cells. Occasionally, large areas of leukocytic infiltration were seen, and in one section one of these areas had undergone necrosis. The alveoli were occasionally filled with edematous fluid staining a pale pink.

Liver: The livers of these dogs showed more marked lesions than did any of the other organs. All the animals, except dog 106, showed necrosis of the central lobules to a greater or less extent, usually marked. In a few cases, there was only

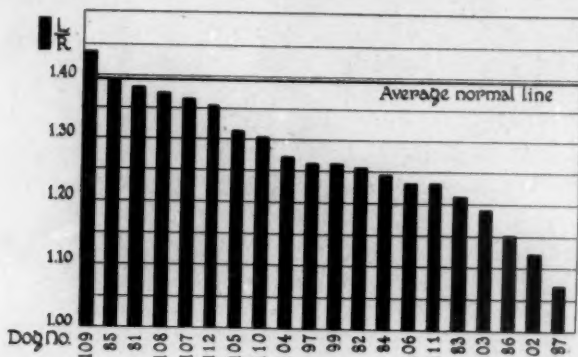


Fig. 2.—Showing the grouping of the L/R ratios, with reference to the average L/R ratio of normal dogs (average normal line). The heights of the solid columns represent the L/R ratios of the dogs that had received diphtheria toxin.

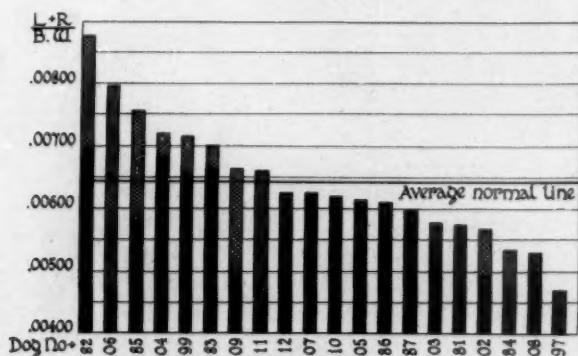


Fig. 3.—Showing the grouping of the $\frac{L+R}{B \cdot W}$ ratios, with reference to the average normal line. The total height of a column represents the $\frac{L+R}{B \cdot W}$ ratio when the weight of the dog at autopsy is used in the calculation of the ratio. The height of the solid column represents this ratio when the weight of the dog before the injection of diphtheria toxin is used in the calculation.

necrosis of a small area of cells in the center, while in others, the necrosis extended half way or more toward the periphery of the lobule. In some sections, there was a marked extravasation of red cells into the necrotic areas. The necrotic cells in many sections were undergoing phagocytosis by Kupffer cells, which contained brown pigment granules. Bile thrombi were occasionally seen. In all sections,

except those of dog 106, there were, in the centers of some lobules, collections of mononucleated cells of varying size and, in many, a few cells having the morphology of nucleated red cells. The nuclei were round and deeply stained, and the surrounding protoplasm was clear pink, or nearly the same tint as that of the red cells in the section. These cells suggested the presence of foci for the formation of new blood in the liver. I could not be certain, however, from examination of the sections that the cells were nucleated red cells. Unfortunately, blood smears were not examined for the presence of nucleated red cells in the circulating blood.

Kidneys: Necrosis of the tubular epithelium was the most common renal lesion observed. The tubules toward the outer limits of the cortex seemed to be most frequently involved. In some sections there were large areas in which all the tubules were necrotic and nuclear elements were not seen, while in other sections, the necrosis was limited to scattered, isolated tubules. In sections from one animal, the tubular epithelium contained large vacuoles. Sometimes, the blood vessels were engorged with red cells, and occasionally there were fresh infarcts. In the sections from dogs 84, 86 and 99 collections of round cells were present in the interstitial tissue. The glomeruli in the kidneys of dogs 85 and 105 were in many places invaded by fibroblasts and round cells. In none of the sections was there a thickening of Bowman's capsule similar to that which Pritchett⁴ observed in guinea-pigs following the injection of diphtheria toxin.

Spleen: Sections were made from the spleens of four dogs. In two of these, pathologic changes were not observed. In the other two, there was marked engorgement with red cells.

Summary.—Following the injection of diphtheria toxin intravenously, the dogs became ill, lost weight and frequently developed jaundice; death occurred from two and a half to twenty-two days after the injection. It was found that the injection of from 0.00135 to 0.00168 cc. of toxin per kilogram of body weight was always followed within a few days by the symptoms described, but the animals receiving the smaller dose survived longer than those receiving the large one. A dosage of 0.001 cc. per kilogram of body weight caused death in only one instance. In the animals receiving this dose the only symptom of intoxication was a loss of weight, which was as great as that in the dogs receiving the larger doses. Studies of the urine showed evidence of irritation of the kidneys, and examination of the urine and the blood plasma of dogs with jaundice showed, in several instances, the presence of bile. The electrocardiograms presented a progressive decrease in the R_s and R_t waves.

At autopsy, ecchymoses were frequently observed in the animals that had received the larger doses of toxin. The most striking of the microscopic observations was the central necrosis of the liver. The necrotic cells were frequently undergoing phagocytosis by Kupffer cells. In some sections there was marked extravasation of red cells into the necrotic areas. In most sections, in the centers of the lobules, collections of mononucleated cells of varying size were observed. Many of these cells had the morphology of nucleated red cells. The heart muscle was particularly lacking in any microscopic lesion that could be attributed to the toxin. The L/R ratios varied between 1.07 and 1.45, and the $\frac{L+R}{B+W}$ ratios between 0.00468 and 0.00874.

4. Pritchett, I. W.: Pathological Effects of Diphtheria Toxin in the Guinea-Pig with Special Reference to a Lesion of Bowman's Capsule, *Am. J. Hyg.* **2**:536, 1922.

COMMENT

The pathologic changes that I observed at autopsy and microscopically in sections from dogs that had received injections of diphtheria toxin did not differ essentially from those reported by other investigators. I made observations, however, of the pathologic physiology that accompanied these changes. Jaundice following intoxication with diphtheria toxin is not frequently mentioned in the literature. It was observed by Courmont, Doyon and Pariot.⁵ In my series it occurred in 66 per cent of the animals into which had been injected a dose of 0.00135 cc. or more of toxin per kilogram of body weight. It seems most likely that the jaundice resulted from destruction of the blood by the diphtheria toxin (Stewart⁶). Courmont, Doyon and Pariot also described the central necrosis of the liver that I found in all the animals receiving 0.00135 cc. or more of toxin per kilogram of body weight. Flexner⁷ observed that the necrotic areas in the liver occurred more frequently in the center of the lobule than toward the periphery, while Du Bief and Bruhl,⁸ in a less extensive report, described scattered areas of necrosis, which were not limited to the central portion of the lobule.

The Heart.—The frequency of sudden death in the course of clinical diphtheria has been the cause of much experimentation on animals in an attempt to discover the mechanism. The sudden death has been commonly supposed to be a direct result of heart failure. However, histologic examination of the heart muscle in patients who have died of diphtheria infection and in experimental animals that have received injections of diphtheria toxin has usually failed to reveal significant changes. MacCallum,⁹ from his experiments, concluded that death occurring at the height of an attack of diphtheria is not exclusively the result of a direct injury to the heart, although this may play some part in the process. He suggested that a vasomotor paralysis may be involved. Marvin and Buckley¹⁰ recently reported anatomic lesions in the ventricular and auricular musculature and in the conduction system

5. Courmont, J.; Doyon, M., and Pariot: Lésions hépatiques engendrées chez le chien par la toxine diphtérique, *Compt. rend. Soc. de biol.* **47**:610, 1895.

6. Stewart, H. J.: A Study of Certain Effects Occasioned in Dogs by Diphtheria Toxin: II. An Analysis of the Mechanisms Possibly Responsible for the Alterations of the Heart, *Am. J. Path.*, to be published.

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8. Du Bief and Bruhl: Note sur une altération des cellules hépatiques dans la diphtérie expérimentale, *Compt. rend. Soc. de biol.* **43**:135, 1891.

9. MacCallum, W. G.: The Mechanism of the Circulatory Failure in Diphtheria, *Am. J. M. Sc.* **147**:37, 1914.

10. Marvin, H. M., and Buckley, R. C.: Complete Heart Block in Diphtheria, *Heart* **11**:309, 1924.

of the heart of a patient who had died of diphtheria. This patient had exhibited complete heart block before death. Numerous cardiac lesions in experimental animals have been described. Flexner⁷ described degenerative changes in the muscle cells, including fatty degeneration, and lesions of the blood vessels. He did not find interstitial changes. Mollard and Regaud¹¹ described minutely changes in the morphology of the muscle cells, such as transverse and longitudinal fragmentation and nuclear degeneration, and changes in the blood vessels. Loth¹² described fatty infiltration and a "cooked appearance" of the muscle fibers in the hearts of guinea-pigs following the injection of diphtheria toxin. A study of my specimens did not reveal lesions of the heart muscle fibers or of the interstitial tissue that could be attributed to diphtheria toxin.

A decrease in the electrical potential as led off in leads 2 and 3 (fig. 1) is observed in the decrease in the amplitude of waves R_2 and R_3 of the electrocardiograms. In all of my animals there was a decrease in the L/R ratio, which may have been reflected in the change observed in the electrocardiogram. The diphtheria toxin may indeed have injured the fibers so that their behavior, as recorded by the electrocardiogram, differed from that of normal fibers. This difference was reflected in the decreased R_2 and R_3 waves. Nevertheless, I was not able definitely to interpret the changes.

In analysis of the data on the weights of the hearts, the figures of Herrmann for normal dogs were used. In his study, Herrmann sectioned the hearts of 200 normal dogs of various species and of about equal numbers of both sexes and calculated the L/R and $\frac{L+R}{B+W}$ ratios. The normal L/R ratio, according to Herrmann,¹³ is 1.393 and the normal $\frac{L+R}{B+W}$ ratio is 0.00635. The L/R ratios of the hearts of the dogs in this series into which diphtheria toxin had been injected varied between 1.07 and 1.45. In all dogs, except dog 109, the L/R ratio was less than the average L/R ratio of normal dogs (fig. 2). This would indicate that the left ventricle lost more weight than did the right ventricle. Taken in conjunction with the $\frac{L+R}{B+W}$ ratios, the change in the

11. Mollard, J., and Regaud, C.: Lésions expérimentales du coeur provoquées par la toxine diphtérique, *Compt. rend. Soc. de biol.* **47**:828, 1895; Lésions chroniques expérimentales du myocarde consécutives à l'intoxication diphtérique, *ibid.* **49**:674, 1897; Contribution à l'étude expérimentale des myocardites: Lésions du myocarde dans l'intoxication aigue par la toxine diphtérique, *Ann. de l'Inst. Pasteur* **11**:97, 1897.

12. Loth, M.: The Heart in Diphtheria: A Clinical and Pathologic Study, *Arch. Int. Med.* **31**:637 (May) 1923.

13. Herrmann, G. R.: Experimental Heart Disease: I. Methods of Dividing Hearts; with Sectional and Proportional Weights and Ratios for Two Hundred Normal Dogs' Hearts, *Am. Heart J.* **1**:213, 1925.

ratio is probably to be ascribed to the loss of weight which took place rather than to an actual right ventricular hypertrophy or a left ventricular atrophy in the short time of a few days. The marked decrease in the size of the x-ray shadow of the heart following the injection of 0.00135 cc. or more of toxin per kilogram (Stewart⁶) is not inconsistent with such a view.

The ratio of the body weight (B W) to the combined ventricular weights (L + R) varied between 0.00468 and 0.00874 (as recorded in tables 1 to 4). Twelve of the ratios were below the average for normal dogs and eight above the average (fig. 3). If the weight of the animal just before the injection of the diphtheria toxin was used in calculating the $\frac{L+R}{B\ W}$ ratio, this ratio was found below the average in sixteen animals and above the average in only four (tables 1 to 4). Since there was a considerable loss of weight by these animals and since it has been shown by Stewart⁶ that loss of body weight does not influence the size of the heart, it was more accurate to use the initial figures in calculating the ratios.

CONCLUSIONS

Diphtheria toxin injected intravenously into dogs produces intoxication and death, if the dose is sufficiently large.

The injection of diphtheria toxin causes jaundice. If the cells in the liver (to which I called attention) are nucleated red cells, jaundice may have resulted from a destruction of red cells.

Central necrosis of the liver occurs when the dose of toxin is 0.00135 or more per kilogram of body weight.

Changes are not observable in the microscopic appearance of the heart muscle. Profound changes do, however, occur in the heart, as shown by the slight changes in the R₂ and R₃ waves of the electrocardiogram, the decrease in the $\frac{L+R}{B\ W}$ ratio, the decrease in the L/R ratio and the decrease in the size of the heart.

THE CAUSE OF DEATH FOLLOWING INTRAVENOUS INJECTION OF OX AND DOG SERUM INTO RABBITS *

JACOB RABINOVITCH

ST. LOUIS

Naunyn¹ observed that the intravenous injection of substances that have the power to destroy the erythrocytes of the animal into which the substances have been injected leads to the formation of intravascular fibrinous thrombi. Landois² was the first to attribute death following the intravenous injection of foreign serums chiefly to the occlusion of small pulmonary vessels by thrombi. He described the center of these thrombi as consisting of agglutinated erythrocytes around which fibrin was deposited. Ponfick,³ on the other hand, denied the occurrence of thrombi following the injection of foreign serums. In this connection, it is of interest to refer to the work of Flexner,⁴ who interpreted hyaline thrombi, found in certain infectious diseases and also produced experimentally by injections of substances that injure the erythrocytes, such as dog serum, ether and ricin, as consisting of agglutinated erythrocytes that subsequently have undergone secondary changes. After intravenous injections of lethal doses of dog serum or ether into rabbits, he found coagula filling the right side of the heart and the large pulmonary vessels. These coagula consisted of agglutinated red corpuscles; the formation of fibrin did not have any part in the origin of these thrombi. Pearce⁵ also attributed the formation of thrombi and subsequent necrosis in the livers of dogs following the intravenous injection of serum of rabbits, which previously had been immunized with material obtained from the blood-containing organs or which had merely received injections of the bile of dogs, to the agglutination of erythrocytes caused by these serums.

Several years later, in continuation of his comparative studies on the coagulation of the blood and on thrombosis, Loeb,⁶ with Strickler and Tuttle, analyzed the cause of death in rabbits after the intravenous

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* From the Department of Pathology, Washington University School of Medicine.

1. Naunyn, B.: *Arch. f. exper. Path. u. Pharmacol.* **1**:1, 1873.

2. Landois: *Die Transfusion des Blutes*, Leipzig, 1875.

3. Ponfick: *Virchows Arch. f. path. Anat.* **62**:273, 1875.

4. Flexner, Simon: *J. M. Research* **8**:316, 1902.

5. Pearce, R. M.: *J. M. Research* **12**:329, 1906.

6. Loeb, Leo; Strickler, A., and Tuttle, L.: *Virchows Arch. f. path. Anat.* **201**:5, 1910.

injection of dog serum or of ox serum. As did Landois, they found, after the injection of the foreign serums, occlusion of the pulmonary vessels by thrombi. However, they did not base their conclusions merely on the microscopic observations in the various organs of the animals into which the serums had been injected, but, in addition, made use of an experimental method that lent a much greater degree of certainty to their interpretation of the microscopic observations than a morphologic investigation alone could have done. By preventing the coagulation of the blood by the injection of solutions of hirudin, Loeb and his collaborators were able to show that, after the injection of dog serum, the rabbit succumbed to the occlusion of the pulmonary vessels by fibrinous thrombi; for hirudin, by inhibiting the development of these thrombi, prolonged the life of the rabbits, and, in a number of cases, prevented death. On the other hand, hirudin was ineffective after the injection of ox serum because the latter substance does not cause the formation of fibrinous thrombi, but of thrombi consisting of agglutinated erythrocytes. These results corresponded with those of experiments *in vitro* in which the action of dog serum and ox serum on rabbit blood was correlated with the symptoms following the injection and also with the microscopic appearances in the organs of the animals that had received the injections. The thrombi following the injection of dog serum were the type of thrombi due to the formation of fibrin, and those following the injection of ox serum were the type caused by agglutination of red cells.

Soon afterward, Zinsser⁷ studied the cause of death following the intravenous injection of goat serum in rabbits; he excluded hemagglutinations as the cause of death, but admitted the possibility that hemolysis was a factor. However, Zinsser did not make use of an anticoagulation substance, nor did he report microscopic observations in the lungs of the animals into which injections had been made. Recently, Aronson⁸ concluded that the hemagglutination and the hemolytic and necrotizing actions of goat serum are due to one and the same substance.

Kusama,⁹ repeating the experiments of Loeb and his collaborators, could not confirm the prolongation of life which the latter investigator had observed when the injections of dog serum were combined with injections of hirudin. Kusama attributed the death following injection of the foreign serum to the increased viscosity of the blood leading to stasis in various organs—without, however, giving any proof of this condition. This author, furthermore, asserted that the increased coagulability of the blood of the rabbit following the injection of dog

7. Zinsser, Hans: *J. Exper. Med.* **14**:25, 1911.

8. Aronson, J. D.: *J. Immunol.* **15**:465, 1928.

9. Kusama, S.: *Beitr. z. path. Anat. u. z. allg. Path.* **5**:55, 1913.

serum was due to disintegration of the blood platelets, and he denied the existence of fibrinous thrombi in this case, as reported by Loeb.

Still another view concerning the death of rabbits following the intravenous injection of foreign serums was expressed by Coca,¹⁰ who interpreted it as due to a constriction of the pulmonary vessels following the intravenous injection of the serum. Coca's view was based on the fact established by Airila,¹¹ Coca and Drinker and Bronfenbrenner¹² that, in animals made anaphylactic through sensitizing injections of a foreign serum, subsequent injections cause a constriction of the pulmonary vessels that leads to the death of the animal. Coca, however, did not carry out experiments in animals not previously sensitized to foreign serums. More recently, Friedberger and Seidenberg¹³ showed that perfusion of the isolated lungs of animals with foreign serums actually leads to a constriction of the pulmonary vessels.

Thus, three views may be distinguished concerning the cause of death following the intravenous injection of foreign serums in rabbits: (1) the view expressed by Loeb, Strickler and Tuttle that death is due to the occlusion of the pulmonary vessels by thrombi following the intravenous injection of hemolytic serums and to the occlusion by agglutination of erythrocytes following the injection of agglutinative serums; (2) the view of Kusama that death is due to increased viscosity of the blood, and (3) the view of Coca that death is due to constriction of the vessels independent of thrombi.

Because of these marked divergencies of opinion concerning the mode of action of foreign serums in causing death after intravenous injection, I repeated and extended in various directions the investigations of Loeb and his collaborators and of Kusama.

EXPERIMENTS WITH OX SERUM

Preparation of Ox Serum for Injection into Rabbits.—The blood was obtained in the slaughter house and was collected in a sterile vessel; the first blood flowing out of the wound was discarded. The blood was allowed to clot and was then kept in the refrigerator for twenty-four hours, during which the clot retracted and the serum separated. The serum thus obtained had, as a rule, a reddish tinge, but became clear after centrifugation. It was found that when the serum was kept continuously in the refrigerator, it remained active for a number of days. Fresh blood, however, was obtained twice weekly so that not at any time was the serum used in my experiments more than four days old. Before injection, the serum was warmed to body temperature; it was then injected under aseptic conditions into the ear vein of a rabbit at a slow rate, usually that of from 3 to 4 cc. per minute.

10. Coca, Arthur: J. Immunol. **4**:219, 1919.

11. Airila, Y.: Skandin. Arch. f. Physiol. **31**:388, 1914.

12. Drinker, C. K., and Bronfenbrenner, Jacques: J. Immunol. **9**:387, 1924.

13. Friedberger, E., and Seidenberg, S.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:276, 1927.

1. *Injection of Lethal Doses of Ox Serum.*—In the large majority of cases, the dose of serum that killed a rabbit within from three to five minutes after its injection ranged from 7 to 8 cc. per kilogram of the weight of the animal. There were, however, occasional variations, depending on the kind of rabbits used, some being more susceptible to the serum than others; e.g., it was found that, in general, gray rabbits were less susceptible than white rabbits.

When a lethal dose of ox serum was injected, the animal became dyspneic almost immediately after completion of the injection, or, at times, even in the course of the injection. This condition was soon followed by gasping for air, a shriek, opisthotonus, convulsions and death.

At autopsy, which was performed immediately after death, I found all the chambers of the heart still beating, at times rhythmically and at other times arrhythmically. The right side of the heart was usually markedly dilated, but gross coagula could not be found in the heart or the larger vessels. The lungs were a normal pink, but showed occasional edema, and possibly areas of a telecystic. The occurrence of edema seemed to depend on the length of time elapsing between the injection and death; in those animals in which death was rapid, i.e., within from three to five minutes after the injection of the serum, edema of the lungs could not, generally, be found. In those cases in which death was delayed to from ten to fifteen minutes after the injection, or longer, edema of the lungs was observed frequently. None of the other organs examined, spleen, liver, kidney, brain, etc., showed any gross pathologic lesions.

The microscopic examination of the various organs revealed serious lesions only in the lungs. There was marked dilatation of the lung capillaries, and these were occluded by hyaline thrombi, which seemed to be composed of agglutinated red corpuscles. Definite outlines of the individual red cells could not be made out in the capillaries. I found only occasional clumps of blood platelets in some of the capillaries. These did not, therefore, seem to play an important rôle in the formation of the thrombi. The larger vessels, particularly the pulmonary veins, were filled with red cells, white cells and some elements that might have been blood platelets. These platelet-like structures, however, lacked definite outlines. I found, also, in the larger veins, disintegrated blood cells that were not unlike blood platelets. A striking feature was the entire absence of any visible fibrin in the capillaries or in the larger blood vessels. This absence of fibrin suggested that the occlusion of the blood vessels by the hyaline thrombi was not due to a process of coagulation, but essentially to an agglutination of the red cells. All the other organs examined microscopically showed merely congestion. The brain failed to present any pathologic lesion that might have accounted for any of the symptoms observed, or for the death of the animal following the injection of the ox serum.

In view of such a widespread occlusion of the pulmonary capillaries, following the injection of a lethal dose of ox serum, it is reasonable to assume that a state of asphyxia developed, owing to the difficulty which the blood had in moving from the right to the left ventricle of the heart. In addition, the diminution in the volume of the alveolar spaces of the lungs, as a result of the great distention of the capillaries, may have intensified the asphyxia. These conditions gave rise to all the symptoms and finally caused the death of these animals. These effects were perhaps still further intensified by the marked stagnation of the blood in all the other organs, especially in the heart, liver, kidneys and spleen.

Injection of Sublethal Doses of Ox Serum.—When, instead of from 7 to 8 cc. of ox serum per kilogram of the weight of the animal, I injected a sublethal

dose, namely, from 4 to 5 cc. per kilogram of weight, the rabbits appeared perfectly well and seemed unaffected by the injection. When these animals were killed within from ten minutes to twenty-four hours after the injection of the serum, I found in the organs that appeared normal to the eye certain microscopic changes much like those I have just described as occurring in rabbits dying after receiving a lethal dose; namely, scattered areas in which the capillaries in the lungs were occluded by hyaline thrombi. However, there existed an important difference between these two groups of animals. Whereas, in the group that had received the injection of lethal doses of ox serum, practically all the capillaries were occluded, in the group that had received the injection of sublethal doses, only a small number of capillaries were affected. This difference in the degree of occlusion of the capillaries in these cases explains the difference between the results obtained with lethal and those obtained with sublethal doses of serum. In the former instance, the more complete occlusion of the capillaries led to the death of the animals, whereas, in the latter instance, the circulation and aeration of the blood were not sufficiently interfered with to call forth any serious symptoms.

These results lead, therefore, to the conclusion that the changes in the vessels of the lungs are responsible for the asphyxia observed after the injection of ox serum; also that the changes noted in other organs are only secondary to the interference with the pulmonary circulation and are, at best, of secondary significance.

Effect of Heparin in the Formation of Thrombi in Rabbits Following Injection of Ox Serum.—In order to find corroborative evidence of the absence of fibrin in the thrombi that form in the capillaries of the lungs after the injection of ox serum, I sought to determine how far intravenous injection of heparin, either preceding the injection or in combination with the latter, influences the results of the administration of this serum. In this connection, it may be recalled that, in his earlier experiments, Loeb had used hirudin for similar purposes and found it ineffective. I injected from 5 to 10 mg. of heparin per kilogram of the weight of the animal, a quantity sufficient to prevent the coagulation of the blood in the rabbit thus treated. I found that the addition of this substance did not prolong the life or prevent the death of the animal after the administration of an ordinarily lethal dose of ox serum. Furthermore, both the macroscopic and the microscopic pictures of all the organs from the animals treated with ox serum plus heparin were exactly the same as those of the organs from animals into which ox serum alone had been injected.

One may therefore conclude that the formation of the thrombi in the capillaries of the lungs following the injection of sufficient amounts of ox serum is a result of an agglutination of the red cells, and does not depend on the formation of fibrin, enveloping and binding together the red cells into a thrombus. If the thrombi that develop after the injection of ox serum were the result of the formation of fibrin, one should expect heparin, which, in the amount injected, has a pronounced anticoagulating effect, at least to retard or, perhaps, prevent altogether the occurrence of the thrombi and the death of the animal.

Changes in the Blood Cell Count in Rabbits into Which Ox Serum Had Been Injected.—Inasmuch as I had assumed that the injection of ox serum leads to a retention of cellular elements of the blood in the lungs and in other organs, but that this does not lead to hemolysis, it was of interest to follow the fate of the blood cells by means of counts of the various elements of the blood, made at different times after the injection of the serum.

In the normal rabbit, the blood counts were as follows: red blood cells from 5,000,000 to 6,000,000; white cells, from 8,000 to 9,000, and blood platelets from 500,000 to 600,000 per cubic millimeter. The platelet count was made according to the method of Reimann.¹⁴ From three to five minutes after the injection of a lethal dose of the ox serum, a definite decrease was noted in all the cellular elements of the blood; the number of the red cells was then from 2,000,000 to 3,000,000; that of the white cells, from 3,000 to 4,000, and that of the blood platelets from 100,000 to 200,000 per cubic millimeter. These animals usually died within from six to seven minutes after the injection of serum.

When a sublethal dose of ox serum (from 5 to 6 cc. per kilogram of the weight of the rabbit) was injected, during the first two minutes following the injection, no marked change was found in the cellular elements of the blood, but after from three to five minutes there occurred a marked reduction in the counts of all the cells. Thus, the red cells were found numbering only from 2,000,000 to 3,000,000, the white cells from 4,000 to 5,000 and the platelets about 150,000 per cubic millimeter. These numbers then diminished continuously until two hours after the administration of the serum, when the minimal count was reached. At this period, the count of the red cells decreased sometimes to less than 1,000,000, while the count of the white cells fell to 2,000 or 3,000 and that of the platelets to 50,000 or 60,000 per cubic millimeter. In other cases, however, the decline in the cell counts after two hours was less pronounced, the red cells numbering about 3,000,000, the white cells 6,000, and the platelets 300,000 per cubic millimeter.

But this great reduction in the cellular elements of the blood was only temporary; counts made twenty-four hours after the injection of serum showed a general tendency of the numbers of blood cells to return again to higher figures. I found, for instance, the number of red cells at that time to be about 4,000,000, of white cells 4,000 and of platelets about 400,000, though the number of all the cellular elements of the blood, while it was increased, was still distinctly lower than normal.

The increase that I found after twenty-four hours must have been largely due to the freeing of the cells that had been retained in the capillaries of the various organs. It is not probable that the red cells that had been agglutinated could secondarily separate from each other. However, the masses of stagnating blood corpuscles that I found shortly after the injection of sublethal doses of ox serum had greatly diminished after twenty-four hours.

These results are interesting in view of the fact that they agree with our conclusion that the cellular elements of the blood are retained in the capillaries, especially in the lungs, but also in other organs, and this retention concerns the red cells, as well as the leukocytes and the platelets.

Immunization of Rabbits Against Ox Serum.—In his experiments, Loeb succeeded in producing in rabbits a marked immunity to the lethal effects of

14. Reimann, H. A.: J. Exper. Med. 40:553, 1924.

dog serum; on the other hand, in preliminary experiments, he found it impossible to produce a similarly pronounced immunity to ox serum. I made some experiments in which I determined whether, through repeated intravenous injections of sublethal doses of ox serum, it was possible to achieve a diminution in the severity of the symptoms following the injection of a lethal dose, and to delay or prevent the death following such an injection.

Five rabbits were used for this purpose, all of which received every second day intravenous injections of ox serum, 4 cc. being injected at the start and then gradually increasing amounts, 5 cc., 6 cc., 7 cc. and 8 cc. per kilogram of the weight of the animal. Of the animals thus immunized which had received injections of a minimal lethal dose of the serum one week following the last immunizing injection, three died about fifteen hours after the injection, while two were still alive twenty-four hours afterward. At this time, the animals were killed and their organs removed for examination.

Sections of the lungs from the immunized rabbits, the life of which had been prolonged, but which died about fifteen hours after the injection of the serum, showed, as a rule, marked edema of the lungs and occlusion of the vessels by agglutinated red cells. This picture was similar to that observed in the nonimmunized rabbits. I also found, in these cases, occlusion of the pulmonary vessels by a material that was either blood platelets or disintegrated red cells. On the other hand, in sections of lungs taken from rabbits that were still alive after twenty-four hours, I found occlusion of the capillaries by agglutinated cells only in certain parts of the lung. The occlusion was therefore less marked in these animals, and edema of the lungs was entirely lacking.

EXPERIMENTS WITH DOG SERUM

Injections of Dog Serum.—In these experiments, the blood was obtained from the jugular vein of a dog, and the serum was separated from it in the manner described in the case of ox serum. The lethal dose of the dog serum was found to be similar to that of the ox serum; namely, from 7 to 8 cc. per kilogram of the weight of the animal. Likewise, the symptoms resulting from the injection of a lethal dose were the same: dyspnea, gasping for air, shrieking, opisthotonus, convulsions and death. At autopsy, performed immediately after the death of the animal, I found the right side of the heart much dilated and the heart chambers of both the left and the right side still beating, sometimes rhythmically and at other times arrhythmically. If death occurred within the first ten minutes after the injection of serum, gross coagula were found in the right side of the heart, extending into the vena cava and the portal vein, as well as into the pulmonary veins. In cases in which death was delayed for longer than ten minutes, clots were not seen in the heart or the larger veins. The lungs did not show, as a rule, any gross pathologic lesion, with the exception of occasional edema, the latter condition depending on the length of the period elapsing between the injection of serum and the death of the animal; the longer this period, the more frequent and extensive was the edema in the lungs. All the other organs examined, spleen, liver, kidneys, brain, etc., appeared normal to the naked eye.

Microscopic examination of the various organs showed the main lesion to be in the lungs, as in the case of the injection of ox serum. The pulmonary changes consisted in widespread dilatation of the capillaries and occlusion by red cells massed-together. While it was difficult to recognize fibrin in the capillaries, in the larger veins deposits of fibrin could readily be seen. A marked hemolysis

of the red cells was also noted; this condition is of interest, especially because it is probably responsible for the formation of fibrin within the vessels.

One may assume, therefore, that the occlusion of the capillaries by thrombi is the cause of death after the injection of dog serum as well as after the injection of ox serum. However, the cause of the formation of the thrombi is not the same in both cases. After the injection of ox serum, one has to deal with thrombi due to agglutination, whereas following the injection of dog serum, the finding of fibrin clots in the larger veins indicates a process of coagulation leading to the formation of fibrinous thrombi.

Effect of Heparin on Rabbits Following Injection of Dog Serum.—In order to test this conclusion, I carried out experiments in which heparin was injected intravenously into rabbits simultaneously with or preceding the injection of dog serum. In these experiments, from 5 to 10 mg. of heparin per kilogram of the weight of the animal was injected. It was then found that, whereas the animals that had not received injections of heparin died within from five to ten minutes after the injection of a lethal dose of dog serum, the rabbits receiving a suitable amount of heparin in addition to the serum lived for a much longer period and in some cases, seemed to be unaffected by the serum up to the moment that they were killed, almost twenty-four hours after the injection. In order to obtain these results, it was necessary to guard against the use of too large a quantity of heparin; in two cases in which 20 mg. of heparin per kilogram of weight was injected, the animals died within fifteen minutes. But, even in these cases, the controls died in a shorter time, namely in from five to ten minutes after the administration of the dog serum. When an excess of heparin was injected, there seemed to be a marked tendency to extensive hemorrhages, especially in the lungs, but also in the liver, spleen and kidney, and it is probably this condition that hastens the death of the animals in such cases. On the other hand, when too small a quantity of heparin was injected, the process of coagulation was not prevented, and there was, therefore, only a temporary delay in the death of the animals, usually extending over several hours.

It was also interesting to note that the microscopic examination of lungs of rabbits that lived for twenty-four hours following combined injections of serum and heparin and were then killed, did not show any noticeable deviation from the normal; there was no evidence of the formation of thrombi in the capillaries or the larger vessels.

When in combination with heparin, a dose of dog serum was injected which, in a rabbit not receiving heparin would have been lethal within from five to ten minutes, but which, under these circumstances, was not lethal, and when this animal was killed at the time when the control animal died, I found in the lungs of the former a complete absence of thrombi, in contrast with what I found in the lungs of the latter: the capillaries and the vessels, as usual, occluded by thrombi.

All these experiments make it evident that the occlusion of the capillaries in the lungs of the animals receiving injections of dog serum is due to the formation of fibrinous thrombi, in which the cellular elements of the blood, especially the red cells, are enmeshed. These masses of

red cells are much paler than the agglutinated erythrocytes that occlude the vessels in the lungs of the rabbits receiving injections of ox serum. This difference is due to the hemolytic action that dog serum exerts on rabbit corpuscles in contradistinction to the action of ox serum, which is essentially agglutinative in its effects. Thus, the thrombi found after the injection of dog serum have the appearance of pale, hyaline, homogeneous masses; the thrombi following the injection of ox serum, which allows a much better preservation of the individual blood cells, show clearly outlined erythrocytes. These results confirm the previous observations of Loeb, who used hirudin instead of heparin. They contradict the negative observations subsequently published by Kusama. The latter's erroneous conclusions are probably to be charged to the fact that he used unsuitable concentrations of the anticoagulant.

Changes in the Blood Cell Counts in Rabbits into Which Dog Serum Had Been Injected.—When lethal doses of dog serum were injected intravenously into rabbits, there resulted a pronounced diminution in all the cellular elements of the blood. Thus, in my experiments, within five minutes after the injection

TABLE 1.—*Effect of an Injection of a Sublethal Dose of Dog Serum on the Blood Cells in Rabbits*

Time of Count	Red Cells	White Cells	Blood Platelets
Before injection of serum.....	5,000,000	9,000	510,000
5 minutes after injection.....	3,150,000	8,600	460,000
30 minutes later.....	3,600,000	10,400
2 hours later.....	3,450,000	7,000
24 hours later.....	3,780,000	17,400	485,000

of the serum the red cells were found to have decreased from an original number of 5,000,000 to 1,500,000, the white cells from 9,000 to 2,000 and the platelets from 500,000 to 150,000. On the other hand, when sublethal doses of dog serum were injected (from 4 to 5 cc. of the serum per kilogram of the weight of the animal) only the erythrocytes showed any significant diminution five minutes after the injection, the white cells and the platelets being only slightly affected. Twenty-four hours later, the number of red cells still remained at the same reduced level, whereas the number of white cells showed, as a rule, a considerable increase over the original number. The number of the platelets remained about normal. The results of the counts are given in table 1.

The results set forth in table 1 as following the injection of a sublethal dose of dog serum are strikingly different from those observed after the injection of a sublethal dose of ox serum; in the latter case, a tendency was shown for all the cellular elements in the blood to return to normal after a period of twenty-four hours.

When heparin was injected in suitable amounts together with an ordinarily lethal dose of dog serum, the animal survived and the blood cells did not show any abnormal quantitative change. The results of the counts are given in table 2.

The question arises as to the manner in which heparin prevents the diminution in the cellular elements of the blood. It may do this indi-

rectly by preventing the formation of fibrinous thrombi in which a certain number of blood cells are caught. Another possibility is that heparin may prevent hemolysis. In order to determine whether heparin has any effect on hemolysis, I carried out experiments *in vitro*.

I first ascertained the minimal quantity of dog serum required to hemolyse, within one minute, 1 cc. of a 5 per cent suspension of rabbit's erythrocytes in 0.9 sodium chloride solution and found it to be 0.8 cc. I then noted that 0.5 cc. of a 5 per cent solution of heparin delayed hemolysis of the mixture of serum and red cells for at least two hours, whereas 3 cc. of the solution of heparin prevented hemolysis altogether.

These experiments showed that heparin is capable of preventing the hemolysing action of dog serum on rabbit blood. The mechanism, therefore, through which heparin, when used *in vivo* together with dog serum, hinders the reduction in the number of cellular elements of the blood, is probably two-fold; it acts by preventing the formation of fibrinous thrombi and, thus, the retention of the blood cells, and also

TABLE 2.—*Effect of an Injection of a Mixture of Heparin and a Lethal Dose of Dog Serum on the Blood Cells in Rabbits*

Time of Count	Red Cells	White Cells	Blood Platelets
Before injection of serum.....	6,990,000	14,600	520,000
5 minutes after injection.....	6,390,000	15,800	500,000
1 hour later.....	6,030,000	15,000
2 hours later.....	6,320,000	9,000
24 hours later.....	6,510,000	12,000	496,000

by inhibiting hemolysis. It therefore prevents the formation of fibrinous thrombi in a double manner: (1) by preventing coagulation of the blood and (2) by exerting a certain protective influence on the erythrocytes so that thrombokinase or tissue coagulin, which induces the process of coagulation, is not set free.

If, now, the effects of dog serum and ox serum on the blood cells of the rabbit are compared, it is found that, when either of these serums is injected in lethal doses, a pronounced reduction of all the cellular elements of the blood results; but that, when these serums are injected in sublethal doses, there is a difference in their effects: Ox serum produces a temporary reduction of all the cells in the blood, which, in the course of twenty-four hours, gives place to a return to normal. Dog serum, on the other hand, produces a noticeable reduction only of the erythrocytes, the white cells and the platelets being little affected within the first few hours after the injection of the serum; there is no tendency on the part of the erythrocytes, after the lapse of twenty-four hours, to reach normal counts again; the white cells, on the other hand, surpass now their original number, and the number of the platelets remains practically unchanged. Furthermore, heparin does not

affect the action of ox serum on blood cells in rabbits; but when it is mixed with dog serum, it prevents the reduction in number of the blood cells. As has been seen, ox serum causes a diminution of the number of the blood cells through the formation of thrombi by a process of agglutination and through retention of the cells in various organs; dog serum, on the other hand, produces corresponding effects by the formation of fibrinous thrombi and by hemolysis. In the case of the injection of ox serum, blood cells which are loosely agglutinated or held back in various organs are, after some time, carried back into the general circulation; but, in the case of the injection of dog serum, a considerable number of erythrocytes have been destroyed through hemolysis, while other cellular elements are firmly retained in the fibrinous thrombi and cannot be restored to the circulation. It is only through prevention of hemolysis and prevention or lessening of the formation of fibrinous thrombi that this loss in the number of blood cells can be forestalled after the injection of dog serum.

While it thus seemed certain from our sets of experiments that the cause of death in rabbits receiving a lethal dose of dog serum is occlusion of the capillaries and larger vessels of the lungs by fibrinous thrombi, there still remained the possibility in the case of ox serum that constriction of the pulmonary vessels might, after all, be the real cause of death, and that the presence of thrombi composed of agglutinated red cells was merely simulated. I attempted, therefore, to determine directly the occlusion of the pulmonary vessels by examining on glass slides thin slices of lung that had been rapidly removed from the rabbits before secondary changes could take place, following the injection of lethal doses of ox serum. By exerting gentle pressure on the lung tissue, I could squeeze out from the vessels numerous thrombi consisting of agglutinated red cells, which were readily seen under the microscope. When the same experiment was carried out with pieces of normal lungs, thrombi consisting of agglutinated erythrocytes could not be squeezed out from the vessels. These results demonstrated, therefore, that thrombi consisting of agglutinated erythrocytes actually do occlude the pulmonary vessels. The results thus corroborated my previous observations according to which the thrombi formed in the capillaries of the lungs by agglutination of erythrocytes are primarily responsible for the death of the animal receiving a lethal dose of ox serum. There remains, of course, in addition to the formation of thrombi, the possibility that, in the case of agglutinative serums, a constriction of the pulmonary vessels may play a certain rôle; but, at best, it could only be a subsidiary one. The microscopic examination of the lungs of rabbits following the injection of ox serum does not show any changes suggesting a constriction of vessels in the lung.

COMMENT

My investigations confirmed the conclusions of Loeb that death in rabbits following the intravenous injection of dog serum and ox serum is, in the main, due to the occlusion of the pulmonary vessels by thrombi, which, in the case of ox serum, are caused by a process of agglutination, and, in the case of dog serum, by the formation of fibrin. In order to distinguish between these two types of thrombi, it was necessary to use microscopic in addition to biochemical methods, and employ anti-coagulative substances, such as hirudin and heparin, which prevent the formation of fibrinous thrombi. If, by means of these substances, it is possible to prevent the death or, at least, prolong the life of the rabbits following the injection of the hemolytic serums, one may conclude that the fibrinous thrombi that occluded the vessels of the lung were the actual cause of death in the animals.

My investigations did not confirm the experimental results and conclusions of Kusama. In particular, I showed that contrary to his observations, heparin, acting in a manner similar to that of hirudin, does delay or prevent the death of rabbits that otherwise would quickly have followed the intravenous injection of dog serum. The changes that I described as occurring in the number of the blood cells under various conditions after the injection of foreign serums, the effect of immunization of rabbits against ox serum and, further, the correlation between microscopic alterations in the lung and the symptoms following the injection of ox serum, all agree with these views.

My conclusions as to the relation between death and the type of thrombi that occlude the blood vessels after the injection of ox serum and of dog serum are, thus, in the first place, based on the perfect correspondence that was found to exist between the amounts of serum injected and the general effects of the injection on the condition of the rabbit, and between the graded gross and microscopic changes that were observed under these conditions in the pulmonary vessels. In the second place, they are based on the differences in the effects of heparin when administered in combination with dog serum and ox serum.

From these two sets of data, I conclude that it is mainly the erythrocytes, either with or without the formation of fibrin, that occlude the capillaries, after the injection of the foreign serums, and that blood platelets, if they play any part at all, are only of minor importance in this process. In the case of dog serum, the erythrocytes occlude the vessels because they are retained there by fibrin, which is set free as the result of the destruction of the erythrocytes; whereas, in the case of ox serum, the erythrocytes are held back in the vessels because they agglutinate with each other.

While, in the case of ox serum, which has essentially agglutinative effects, the use of heparin, in accordance with expectations, did not

prevent the death of the animal, I showed that here thrombi due to agglutination actually did occlude the pulmonary vessels. However, I could not definitely exclude the possibility that a constriction of the vessels may not be an additional factor in the death of the animal following injection of ox serum, although I did not find any fact making for such a conclusion.

SUMMARY

Death in rabbits following intravenous injections of either ox serum or dog serum is due primarily to massive occlusion of the lung capillaries by thrombi, and secondarily, perhaps, to the stagnation of blood in other internal organs. There is a possibility that, in the case of ox serum, constriction of blood vessels may be an additional factor, although I did not find any definite indication that this is the case.

Injections of ox serum produce thrombi in the lung capillaries by a process of agglutination, whereas injections of dog serum produce them by causing the formation of fibrin. In agreement with this conclusion is the fact that heparin does not have any effect in preventing the formation of thrombi in the case of injections of ox serum, but is effective when used in combination with dog serum; also that heparin does not prolong the rabbit's life when used in combination with ox serum.

The injection of a lethal dose of either ox serum or dog serum results in a pronounced diminution in the numbers of all the cellular elements of the blood in the peripheral circulation. The injection of sublethal doses of serum, however, in the case of ox serum, brings about a reduction in the number of blood cells only temporarily. In the case of dog serum, the reduction is more permanent. The differences in the quantitative changes in the cellular elements of the blood following the use of these two serums, as well as the differences in the action of heparin on these changes, are in accordance with the difference in character of the thrombi formed after the injection of the two serums. In addition, I found that heparin exerts a certain inhibitory effect on the hemolysis of rabbit's erythrocytes which normally takes place under the influence of dog serum.

THE COARSER HISTOLOGIC VARIATIONS OF THE THYROID GLAND*

JOSEPH McFARLAND, M.D.

AND

GEORGE M. ROBSON, M.D.

PHILADELPHIA

That the microscopic appearances of supposedly normal thyroid glands are subject to considerable variation is well known, but whether the variations of its various appearances can be systematized and correlated with the ages, the physiologic conditions or the morbid states of the patients from whom the glands are taken, does not seem to have been adequately investigated.

It was therefore decided to make a preliminary survey of the subject by a careful study of such variations as might be discovered in 100 glands that did not present any signs of local disease, and had been taken from patients of various ages who died of many different diseases.

MATERIAL

Most of the material was obtained at necropsies performed in the Philadelphia General Hospital, where the greater number of the patients are of advanced age and die of chronic diseases. The age, sex and color of the patients from whom the material was collected are set forth in table 1. The diseases causing death in the patients are shown in table 2.

As scarcely any death from disease can be referred to a single factor, and as the greater the age the more numerous the contributing factors are apt to become, it was impossible to reduce this tabulation to desirable simplicity. For example, some patients with cardiovascular disease had syphilis; the patient dying suddenly of a ruptured aneurysm, of course, had syphilis and vascular disease. When, in such cases, a distinctive appearance of the thyroid was discovered the question arose: To which of the associated conditions was it to be attributed? In the investigations to be considered, we attempted to overcome this difficulty by making many subordinate groups—one, indeed, for every morbid condition mentioned in the necropsy protocols as having been found in the body from which the tissue was derived—and examining each group separately to see whether or not the microscopic variation seemed to occur frequently in it.

Thus a gland from a patient, aged 70, with advanced cardiovascular disease and cancer of the breast, who died of bronchopneumonia, was tabulated in the appropriate age group with all the other glands taken from persons of the same age group; in the cardiovascular group with all the other glands from persons with cardiovascular disease, irrespective of age, other disease or cause of death; in the carcinoma group with all the other glands taken from persons with carcinoma,

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* From the McManes Laboratory of Pathology of the University of Pennsylvania.

irrespective of associated and complicating diseases, and in the bronchopneumonia group with all the other glands taken from persons with bronchopneumonia, irrespective of other factors that might have been contributory to the terminal condition.

The thyroid tissues, as they were collected, were placed in neutral formaldehyde for fixation, and subsequently embedded in celloidin for cutting, because experience

TABLE 1.—*Sources of the One Hundred Thyroid Glands Examined in This Study*

Life Decade	Male	Female	White	Black	Total
1.....	2	2	3	1	4
2.....	1	1	1	1	2
3.....	8	6	6	8	14
4.....	9	2	3	8	11
5.....	16	8	12	12	24
6.....	11	6	13	4	17
7.....	13	6	12	7	19
8.....	12	5	13	4	17
9.....	0	1	1	0	1
Total.....	72	37	64	45	109

TABLE 2.—*Diseases Causing Death in the Patients Whose Thyroid Glands Were Examined*

Disease	Male	Female	White	Black
1. Acute Cases: Noninfectious				
Alcoholism with delirium tremens.....	1	0	1	0
Acute nephritis.....	1	0	0	1
Abdominal actinomycosis; death due to surgical operation.....	1	0	0	1
Subacute glomerular nephritis following burns.....	0	1	1	0
Ruptured aortic aneurysm.....	1	0	0	1
2. Acute Cases: Infectious				
Lobar pneumonia.....	8	1	6	3
Acute cerebrospinal meningitis.....	1	0	1	0
Confluent bilateral bronchopneumonia.....	0	1	0	1
Erysipelas.....	1	1	2	0
Acute peritonitis.....	1	1	2	0
Pyemia with multiple abscesses.....	0	1	1	0
Empyema.....	1	0	1	0
Acute endocarditis.....	2	0	1	1
3. Chronic Cases				
Pulmonary tuberculosis.....	16	5	10	11
Suprarenal tuberculosis.....	1	0	0	1
Cardiovascular disease.....	20	10	10	11
Syphilis.....	7	1	2	6
Carcinoma.....	5	5	5	5
Sarcoma.....	4	2	5	1
Chronic infections (not tuberculous).....	3	1	2	2
Chronic wasting diseases (not tuberculosis or cancer)	1	2	3	0
4. Pregnancy.....	0	2	1	1
5. Obesity.....	0	1	1	0

showed that sections so prepared gave uniform slices of the colloid in the alveoli, while paraffin commonly gave such fractured sections of the colloid that satisfactory study of any peculiar appearances was prevented.

OBSERVATIONS

Significance of Variation in the Color of the Thyroid Glands.—When the blocks were ready for cutting, they showed a variety of different

colors that had not been so distinct in the fresh material. It was possible to arrange the blocks in groups—cream colored, reddish amber, grayish yellow, gray-brown, tan-brown, grayish, yellow-amber, gray and brown—and it was expected that at least some of these color groups would correspond with some of the clinical groups. Comparisons were made by every means that could be devised, but it was impossible to correlate the color groups with the clinical groups, and it seemed therefore certain that the observed variations in color had nothing whatever to do with age, sex, race or morbid condition in the patients from whom the tissues were obtained at autopsy.

It had been suggested that variation in the appearance of the thyroid glands has something to do with the time of year at which they are collected. Nearly all these tissues were obtained during the months of December, January and February. As fifteen of them, collected during May, showed just the same variations, the suggestion of a relation between the variations in color and the time of the year was thought to be a mistake.

Significance of Variations in Texture.—Some of the sections were soft and could be cut evenly and thinly, while others were hard and were cut with difficulty, the knife tending to ride over the tissue rather than to pass through it, so that only thicker sections might be prepared. A few of the sections were "gritty" apart from calcified blood vessels, which were rather frequent.

Although it was suspected that this hardness might be referred to overfixation or prolonged dehydration of the tissues, it seemed as though it might be due to some unknown inherent difference in the colloid. These differences were, therefore, carefully recorded and compared with the various clinical groupings. There was apparently no correspondence. Soft and hard tissues were found associated with all ages, both sexes, both races and all the disease groupings.

Significance of Variations in Structure.—When the cut sections were examined with the naked eye, and then with a hand lens, forty-seven of them appeared to be similar; i.e., their substance was not divided up by noticeable connective tissue partitions, and it seemed to be made up of a parenchyma composed of alveoli of much the same general appearance, containing much the same average quantity of colloid of about the same uniform appearance. Under the microscope, these sections corresponded with the usual "textbook" pictures of the normal thyroid. It was tentatively assumed that this appearance was "normal," and that, on comparison of these apparently normal tissues with the clinical groupings, these glands would be found to have come from patients of about the same age who had died with much the same pathologic disturbances. This proved to be entirely erroneous: thyroid glands of this "normal" appearance were found to have come from

patients from 1 month to 79 years of age, in proportions corresponding with the proportionate distribution of the total number of cases in each decade; of the whole number, twenty-six were from patients less than 50 years of age, twenty-one from patients more than 50 years of age; twenty-three were from patients between 40 and 70 years of age. The average age for the whole group of patients from whom these "normal

TABLE 3.—*The Incidence of the Apparently Normal Thyroid Glands with Reference to the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Causes of Death		Incidence of Apparently Normal Thyroid Glands
1. Acute Diseases		
Infections.....		7
Pneumonias.....		13
		— 20
2. Chronic Diseases		
Cardiovascular-renal diseases.....		13
Tuberculosis.....		6
Syphilis.....		5
Carcinoma.....		2
Sarcoma.....		1
		— 27
		47

TABLE 4.—*The Incidence of the Thyroid Glands That Were Divided into Lobules by Distinct Fibrillar Partitions, with Reference to the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Causes of Death		Incidence of Thyroid Glands Divided into Lobules by Fibrillar Partitions
1. Acute Diseases		
Infections.....		4
Pneumonias.....		5
		— 9
2. Chronic Diseases		
Cardiovascular disease.....		3
Tuberculosis.....		7
Syphilis (with cardiovascular disease).....		4
Carcinoma.....		3
Sarcoma.....		1
Senile weakness after fracture (age of patient, 83) ..		1
Amyotrophic lateral sclerosis.....		1
		— 20
		29

glands" came was 49 years. The glands were referable also to the sexes in proportions corresponding with the proportionate distribution of the total number of cases to each sex: male 36, female 12.

The disappointing results of the attempt to correlate these "normal" thyroid glands with the causes of death are shown in table 3.

Twenty-nine thyroid glands showed the structure to be divided into lobules by distinct and sometimes coarse fibrillar partitions. Our attempt to correlate these with the various groups was slightly more

successful. It is true this condition was observed in patients varying from 1 year to 83 years of age, but the average age was 50 years, and only seven persons were less than 40 years old, twenty-two being over 40. Of these, eighteen were males and eleven were females. Nineteen were white persons and ten black. The correlation of these thyroid glands with the causes of death is set forth in table 4.

Unlike the apparently normal thyroid glands, two thirds of the cases in which fibrillar partitions occurred were definitely in the group of chronic diseases, though the classification was difficult, as one of the patients included in the group of those with chronic tuberculosis died of erysipelas, an acute infection; and one in the group of patients with bronchopneumonia, a person with a long-standing case of hemiplegia, may have had both syphilis and cardiovascular disease.

Significance of Variations in the Appearance of the Colloid.—Under the microscope, the colloid was given careful attention, and was found to present a greater variation in appearance than was expected. The tissues were grouped, with respect to the appearance of the colloid, as follows:

1. The colloid in all the alveoli appeared to be uniform in substance.
2. It differed in density (? color) in different alveoli.
3. It was dense (dark colored) in occasional alveoli.
4. Some of the colloid collections were laminated.
5. The colloid was noticeably vacuolated.
6. Many of the colloid collections contained large vacuoles.
7. Many of the colloid collections contained great numbers of small vacuoles.
8. The colloid appeared to be melting away at the edges of the collections.

Each group was separately gone over with reference to age, sex, race and morbid conditions, as put down heretofore, but in not one could the peculiar appearance of the colloid be made to correspond with any given clinical condition. As nothing came of these attempts, it seems unreasonable to burden the reader with further details and tabulations.

Significance of Variations in Alveolar Space.—There remained the investigation of the size of the alveoli. At first, with the eye as guide, the sections were grouped according to the following scheme:

1. The alveolar spaces contained no colloid substance.
2. They contained little colloid.
3. They contained unequal quantities of colloid.
4. The size of the alveolar spaces and the quantity of colloid that they contained were fairly uniform in the same lobules, though they varied in different lobules.
5. The alveoli contained an apparent excess of colloid.
6. There were occasional small colloid cysts.

As the sections were first gone over, it seemed easy to refer each to one or the other of these groups; but later, when section was compared with section, it was necessary to reassign many of them, and still later to make further changes, until it seemed that, except for groups 1 and 6, a satisfactory arrangement could never be made unless a method of measuring the alveoli could be adopted.

It was then decided to make camera lucida tracings of representative fields of a section of each gland, in the hope that, by comparing these, some accurate grouping could be effected; but this also proved unsatisfactory. The tracings outlined the alveolar lumina, which almost invariably were filled or partly filled with colloid. It was obvious that the glands with many closely set alveoli contained a much greater proportionate volume of glandular space and colloid than did those with fewer and more widely separated alveoli. It also seemed probable that the average size of the alveoli varied much from gland to gland, although the frequent great variation in size within individual glands made the visual estimation of this uncertain. The study of these tracings next suggested that the measurement of the alveolar space as traced might make possible an interpretation of these variations. Thinking of the thyroid gland as a porous body containing many epithelium-lined spaces (the alveoli), we perceived that if we could determine the average size of the alveoli in a given portion of each gland, we could then calculate the proportion of each gland represented by the colloid-filled lumina—a sort of "index of porosity." Such measurements would be indicative of the relative amounts of colloid contained in the respective glands. These amounts obviously varied greatly. If values could be obtained, one could then decide whether this variation was correlated with age or with clinical pathologic groups. The most accurate method of arriving at such values would be by serial sections and reconstruction. This method, however, because of the tremendous amount of labor that it required, was out of the question. After careful consideration, we decided that an estimation of the percentage of alveolar area as seen within the tracings of the alveolar outlines in a given area of each gland would give an index of the proportion of alveolar lumen to total gland. Such a procedure would simply express in a numerical scale the variations in the microscopic sections and tracings, which were so obvious to the eye but so difficult to evaluate by the eye alone.

The following procedure was adopted. Camera lucida tracings from sections of each gland were carefully made, the pencil's point following the epithelial lining of the alveoli. These tracings were made at a standard magnification of 63.5 diameters. Each tracing was of a measured area—usually 20 square inches, which corresponded to an area of $\frac{9}{1000}$ square inch of a microscopic section. In cases in which the picture was not uniform through the section, several or larger areas were traced to insure a representative picture. This gave us tracings of a measured representative area of each gland, showing the outline of the lumen of every alveolus in this area. The surface area of each alveolar space in these tracings was measured. The total area of each field being known, it was possible, by taking the sum of all the alveolar areas in each field and comparing this with the total area of the field, to determine the relative percentage of alveolar space and the relative percentage of intervening tissue. The average size of the alveoli was also determined for each gland by counting the number of alveoli and dividing the total alveolar space by this number.

The method of measurement was by superimposing paper, ruled to $\frac{1}{100}$ square inch, on a tracing and counting the little squares within each alveolar outline. Such squares as were cut by the margins were counted if half or more fell within the outline. Before the adoption of this method, an attempt was made to measure

the areas within the alveolar outlines by use of a planimeter, but many were so small that accurate measurement could not be made with the available instruments. The results were not reduced to scale, because the purpose was not to determine absolute values but to obtain comparable values. The following is an example of the data obtained in the measurement of one gland in this way:

Total area traced	23.46 sq. in.
Number of complete alveoli	188
Number of incomplete alveoli (those cut by the margin of the tracing)	24
Sum of areas of complete alveoli	6.60 sq. in.
Sum of areas of incomplete alveoli	0.82 sq. in.
Total alveolar area (or "open space")	7.42 sq. in.
Percentage of alveolar open space	31.7
Percentage of intervening tissue	68.3
Average size of alveoli	0.04 sq. in.

Several comments should be made at this point concerning the data thus obtained. First, serial sections were not made in any cases, three or four sections being the most studied from any one gland, and all these being cut from one block of tissue. We cannot, therefore, determine mathematically the reliability of the data nor prove that the sections and tracings were representative. The sections, however, were taken from corresponding portions of the various glands, and tracings sufficiently large to be representative of each were made and measured. We believe that, granting a fairly large error, the data are sufficiently reliable to form the basis of the comparisons that follow. Secondly, it is well to recall just what was measured and what is meant by "alveolar space" or "alveolar open space." It was that area included within the traced alveolar outlines made by following the inner margin of the lining epithelium. In the tracings, only alveoli with definite lumina appeared. Empty alveoli without appreciable lumina were not traced or measured. This means that the intervening tissue was not always stroma, but included small empty alveoli, when present. This is well illustrated by the data on a gland from a 2 days old, probably premature, infant. The microscopic picture was that of a fetal thyroid gland without any alveoli containing colloid, and little connective tissue stroma. The alveolar open space was zero, the average size of the alveoli was zero, and the intervening tissue was 100 per cent. These data also show that the average size of the alveoli was based on those with definite lumina, almost invariably containing colloid.

Camera lucida tracings from 100 of the thyroid glands discussed in this paper were made and measured. For each gland, two values were finally calculated: (1) the percentage of alveolar open space, and (2) the average size of the alveoli.

The data obtained by measurement of the alveolar space are given in table 5. The first value is, as has been explained, an index of the glandular space. This factor would seem to be of importance, because it is known that the colloid stores iodine. For this reason, and because the value of this factor showed such wide variations (from 0.8 to 92 per cent), we thought that it might be correlated with age or with pathologic conditions found at autopsy.

TABLE 5.—*The Percentage of the Alveolar Space and the Average Sizes of the Alveoli of Thyroid Glands Taken from Eighty-Three Patients at Autopsy*

Number	Age, Years	Alveolar Space, per Cent	Average Size*	Number	Age, Years	Alveolar Space, per Cent	Average Size*
1.....	2 days	0.0	0.0	51.....	50	54.4	9.8
2.....	1 mo.	43.8	5.4	52.....	50	28.6	2.4
3.....	5	25.0	1.7	53.....	53	25.8	5.9
4.....	6	32.1	2.0	54.....	53	20.6	1.7
5.....	11	43.2	3.2	55.....	54	31.7	4.0
6.....	12	62.3	4.5	56.....	54	54.9	8.8
7.....	17	39.7	7.0	57.....	54	34.7	5.0
8.....	20	61.6	8.3	58.....	55	24.6	2.0
9.....	20	77.1	21.4	59.....	55	54.8	3.4
10.....	22	26.4	8.6	60.....	56	52.0	5.0
11.....	22	45.0	6.3	61.....	57	27.8	3.6
12.....	23	52.4	11.0	62.....	58	68.9	9.2
13.....	24	47.0	3.4	63.....	58	34.3	2.6
14.....	24	31.4	2.2	64.....	58	66.6	13.2
15.....	25	48.4	6.0	65.....	60	24.6	9.1
16.....	26	46.4	11.6	66.....	60	24.3	2.2
17.....	27	74.2	43.0	67.....	60	54.3	7.4
18.....	27	59.7	6.9	68.....	60	45.7	5.7
19.....	27	61.7	5.4	69.....	62	10.8	3.0
20.....	28	46.6	4.2	70.....	63	52.0	4.0
21.....	30	42.2	3.0	71.....	63	48.2	3.1
22.....	32	39.1	5.0	72.....	64	59.0	14.0
23.....	35	31.7	3.8	73.....	64	41.3	4.2
24.....	35	63.9	9.1	74.....	65	35.5	4.0
25.....	37	19.4	1.8	75.....	65	44.3	5.1
26.....	38	53.0	6.3	76.....	65	66.5	9.9
27.....	38	57.7	9.6	77.....	65	35.9	3.1
28.....	38	29.3	3.9	78.....	66	35.5	6.5
29.....	38	28.8	4.6	79.....	68	58.2	4.2
30.....	39	32.8	2.2	80.....	68	40.1	4.0
31.....	40	70.9	8.9	81.....	68	13.2	1.3
32.....	41	33.2	5.6	82.....	69	49.5	6.3
33.....	42	26.4	5.4	83.....	70	35.5	4.3
34.....	42	50.7	9.0	84.....	70	54.8	12.7
35.....	42	73.5	26.8	85.....	70	23.8	1.1
36.....	44	55.9	10.7	86.....	71	36.3	5.8
37.....	44	33.1	5.7	87.....	72	41.8	6.0
38.....	44	17.6	2.8	88.....	72	37.3	4.0
39.....	45	25.6	2.2	89.....	72	47.0	6.4
40.....	47	51.8	10.3	90.....	73	39.6	4.1
41.....	47	33.0	4.0	91.....	73	52.6	12.0
42.....	47	40.5	5.0	92.....	74	43.2	6.6
43.....	49	57.6	5.5	93.....	74	52.0	3.0
44.....	49	12.9	2.6	94.....	75	53.3	10.5
45.....	49	63.9	8.2	95.....	77	60.9	6.4
46.....	49	45.5	7.1	96.....	77	33.0	6.3
47.....	49	46.9	2.1	97.....	77	29.7	7.0
48.....	49	51.9	5.5	98.....	78	29.0	5.0
49.....	50	63.2	10.3	99.....	78	47.0	8.0
50.....	50	92.0	75.0	100.....	83	34.3	4.0

* In hundredths of a square inch.

In order to determine the presence or absence of any correlation between alveolar open space and age or disease, the data were analyzed according to the following rules:

1. Determine the arithmetical mean for the whole series of 100 cases (the "series mean").
2. Determine the arithmetical mean of each of the groups (age groups, by decades, and disease groups).
3. Adopt the series mean from step 1 as the normal standard for comparison.

4. Determine the difference between each group mean and the series mean.
5. Calculate a significant difference for $P = 0.05$ in each comparison, following Fisher's method,¹ by the formula:

$$\text{Significant difference} = \frac{\sqrt{\frac{\sum d_1^2 + \sum d_2^2}{n_1 + n_2 - 2}} \times t}{\sqrt{\frac{n_1 \times n_2}{n_1 + n_2}}}$$

when— $\sum d_1^2$ = the sum of the squares of the deviations of the first series;
 $\sum d_2^2$ = the sum of the squares of the deviations of the second series;
 n_1 = number of observations in first series;
 n_2 = number of observations in second series; and
 t = factor from Fisher's table IV for $P = 0.05$.

6. Compare the "significant difference" as determined thus with the observed difference to estimate its probable significance.

The calculation in step 5 gives the magnitude of a difference that is 95 per cent probable ($P = 0.05$), that is, a difference of such a size as would occur by chance only once in twenty trials. This degree of probability is usually adopted as the limit of significance. Therefore, if a given observed difference is less than this calculated significant difference, it is not regarded as significant; but if it is equal to or greater than this figure, it is considered significant. In estimating the significance of the differences, the standard or probable errors of these differences could have been used, but it was thought that Fisher's method was more suitable because of the small number of observations.

In table 6, the mean percentage values for the alveolar open space for each decade are compared with the series mean (43.3 per cent). In the fourth column, the observed differences are given. By simple inspection of these, it was seen that, except for the first three decades, the differences were small. It appeared from superficial examination that, in the first decade, the mean value of the alveolar open space was decidedly less than the mean for the whole span of life. In the second decade, this value seemed to rise above the average and then to fall through the third decade to a level approximately equal to the series mean for the remainder of life. However, when these observed differences were compared with the calculated significant differences, it was seen that only in the case of the first decade did the observed difference equal or exceed the significant difference. For this decade there were only four glands, one of which (that of an infant, aged 2 days) gave a value of zero. In so small a series, this one value had an undue weight on the mean. Also, the case was questioned because of the probable prematurity of the infant. With this doubtful case omitted, the mean for this decade was 33.1, giving a difference from the series mean of

1. Fisher, R. A.: *Statistical Method for Research Workers*, London, Oliver & Boyd, 1925, p. 109.

10.2. On recalculation, the significant difference of 18.1 was obtained. It was therefore evident, from table 6 and the considerations set forth, that our figures failed to show any significant variation of alveolar open space with relation to age. The reader will undoubtedly note that in the tables comparatively few cases are given for the early decades. The thyroid glands were collected from routine autopsies, without regard to age, because the investigation of variations in the thyroid gland with reference to age was not the primary object of the study.

TABLE 6.—Mean Percentages of the Alveolar Open Space in Thyroid Glands Grouped with Reference to the Ages of the Patients from Whose Bodies the Glands Were Taken at Autopsy

Groups	Number of Cases	Mean	Difference from Series Mean	Significant Difference $P=0.05$ (after Fisher)
Whole series.....	100	43.3
Decade				
First.....	4	25.5	+17.8	16.1
Second.....	5	54.8	-11.5	14.1
Third.....	12	48.5	- 5.2	9.3
Fourth.....	10	42.7	+ 0.6	10.4
Fifth.....	21	45.7	- 2.4	7.7
Sixth.....	16	40.4	+ 2.9	8.5
Seventh.....	17	41.4	+ 1.9	8.5
Eighth.....	15	42.5	+ 0.8	8.3

TABLE 7.—Mean Percentages of the Alveolar Open Space in Thyroid Glands Grouped with Reference to the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy

Groups	Number of Cases	Mean	Difference from Series Mean	Significant Difference $P=0.05$ (after Fisher)
1. Tuberculosis.....	18	40.4	+ 2.9	8.0
2. Cardiovascular disease.....	31	45.2	- 1.9	6.4
3. Acute infection.....	15	45.9	- 2.6	8.5
4. Rapid deaths from other causes.....	5	33.3	+10.0	14.6
5. Tumors.....	17	45.6	- 2.3	8.7
6. Chronic nontuberculous infection....	4	51.8	- 8.5	15.3
7. Chronic wasting diseases.....	6	41.6	+ 1.7	10.4
8. Syphilis.....	10	41.8	+ 1.5	10.3
9. Bronchopneumonia.....	29	41.9	+ 1.4	6.6

In table 7, the mean percentages of alveolar open space for the disease groups are compared with the series mean. Here the differences between the group means and the series mean were small, except in groups 4 and 6. However, even in these groups, the observed differences (column 4) were much smaller than the calculated significant differences (column 5). The percentage of alveolar open space obviously was not correlated with the disease groups given. Further analysis of the larger groups by subdivision into decades, as was done for the whole series, failed to show any variation with age within these groups.

The analysis of our data to this point failed to reveal any significant variation in percentage of alveolar open space in relation to age or

pathologic condition. As a further check, the 100 cases of the series were grouped in a frequency table according to percentage of alveolar open space, an interval of 10 and the midrange values of 5, 15, 25, etc., being used. The results are shown in table 8. Eighty-eight of the glands fell in the groups from 25 to 65, inclusive. In the third column of the table, the average ages for these groups are given. They all fell in a range of five years. The average age for the whole series was

TABLE 8.—*The Average Ages for Different Percentages of Alveolar Open Space*

Percentage Alveolar Open Space Midrange Values	Number of Cases	Average Age, Years
5	2
15	5
25	16	47.4
35	21	51.5
45	21	47.5
55	21	51.4
65	9	62.1
75	4
85	0
95	1

TABLE 9.—*The Average Size of the Alveoli in Thyroid Glands Grouped with Reference to the Age and the Diseases of the Patients from Whose Bodies the Glands Were Taken at Autopsy*

Group	Number of Cases	Mean	Probable Error	(B) Probable Error of		
				(A) Difference	Difference	A ÷ B
Whole series.....	100	7.1	1.3
First decade.....	4	2.3	1.8	4.8	3.1	1.5
Second decade.....	5	8.9	2.9	1.8	3.1	0.6
Third decade.....	12	9.3	2.5	2.2	2.7	0.8
Fourth decade.....	10	5.5	1.7	1.6	2.0	0.8
Fifth decade.....	21	10.3	1.9	3.2	2.2	1.5
Sixth decade.....	16	5.5	1.6	1.6	2.0	0.8
Seventh decade.....	17	5.3	1.6	1.8	2.0	0.9
Eighth decade.....	15	6.3	1.3	0.8	1.6	0.5
Tuberculosis.....	18	5.0	2.5	2.1	2.7	0.8
Cardiovascular-renal disease.....	31	6.2	2.2	0.9	2.0	0.5
Acute infection.....	15	9.3	2.5	2.2	2.7	0.8
Rapid deaths.....	5	5.2	2.6	1.9	2.8	0.7
Tumors.....	17	10.9	2.0	3.8	2.3	1.7
Chronic nontuberculous infection.....	4	5.2	5.3	1.9	5.4	0.4
Chronic wasting diseases.....	6	4.9	1.4	3.2	1.8	1.8
Syphilis.....	10	7.3	1.7	0.2	2.0	0.1
Bronchopneumonia.....	29	7.5	1.9	0.4	2.2	0.2

47.8 years, which is close to all the group values. This was added evidence of the lack of a correlation between percentage of alveolar open space and age.

The determination of the relative sizes of the alveoli also proved to be of no significance. The variations in size within each gland resulted in large errors for the mean values. These errors in conjunction with those of the group and series means robbed the results of all significance. Table 9 gives the mean alveolar sizes for the series and the groups, by decades and diseases. The means and the probable errors of the means (calculated as 0.67 of the standard deviations) are given in columns 3

and 4. The observed differences from the series mean are shown in column 5 with the probable errors of the differences in column 6. In no case did the observed difference between the series mean and a group mean equal twice the probable error of the difference. This is shown in the last column, the figures of which were obtained by dividing the observed differences by the probable errors of these differences. This indicates a lack of significance in the differences measured by a less exacting standard than that used in treating the percentage of alveolar open space. Fisher's method, which would serve only to emphasize this lack of significance, was not applied to these data because it would have been a needless expenditure of time to do so.

CONCLUSIONS

A preliminary study of 100 thyroid glands was made for the purpose of determining whether variations in their histologic appearances could be referred to age, sex, color or disease in the persons from whom they were obtained.

Color variations in the blocks of fixed tissue were marked, as was also the ease or difficulty with which they could be cut; but none of these characteristics could be correlated with the clinical conditions of the patients from whom the tissues came.

The "textbook" appearance was shown by sections of forty-seven of the glands. Although it was expected that they would have come from the bodies of patients of about the same age who died of similar diseases, they were found to be from bodies of patients of all ages and of a variety of morbid states.

Twenty-nine glands showed connective tissue trabeculation. Of these, twenty came from bodies of patients who had died of chronic diseases and only nine from the bodies of those who had died of acute diseases.

Numerous variations in the appearance and condition of the colloid were studied, but not one could be found to correspond with any pathologic condition of the patient.

A method was devised by which it was possible to measure the alveolar space, both on the average and in the aggregate, but a statistical analysis of the data so obtained failed to show any correlation with age or disease groups.

As the study of 100 cases by these various means showed nothing, it was not considered worth while to continue the research.

The results indicate that, with the single exception that chronic disease of the patient frequently leads to trabeculation, the grosser histologic variations of the thyroid gland in man do not afford any information with respect to the age, the sex, the color or the morbid condition of the patient.

THE BLOOD PLATELETS IN TYPHUS FEVER *

HOBART A. REIMANN, M.D.

GEORGE Y. C. LU, M.D.

AND

C. S. YANG, M.D.

PEKING, CHINA

There is at present an uncertainty regarding the form of the virus of typhus fever in the blood stream, but strong evidence exists that the virus is represented by *Rickettsia prowazeki*. Since the rickettsiae associated with heartwater disease¹ and Rocky Mountain spotted fever² have been demonstrated free in the blood stream, it is reasonable to suppose that *Rickettsia prowazeki* may be similarly distributed. However, from the results of early experimental studies on typhus fever, it was believed that the virus was intimately associated with the circulating blood cells, either the leukocytes or the platelets.

The observations of several investigators indicated that the virus of typhus fever was closely associated with the blood platelets. Kusama,³ in 1919, was led to this conclusion by the fact that the platelets obtained from the blood of a monkey suffering from experimental typhus fever induced typhus fever when injected into a normal monkey, but that the supernatant plasma from the same sample of blood failed to do so. To demonstrate that the virus was actually contained in the platelets and not merely simultaneously sedimented by virtue of a similar specific gravity, he ground the platelets with the powder of a filter candle.⁴ After half an hour's centrifugation, following this procedure, it was found that the supernatant fluid induced typhus fever in monkeys. Kusama concluded from this experiment that the virus was present in the platelets and was liberated by the process of grinding.

Ségal⁵ and Arkwright and Bacot⁶ concurred in the opinion that the virus of typhus fever is intimately connected with the blood platelets, and that a high concentration of the virus can be realized in the platelet sediment by the centrifugation of citrated blood.

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* From the Department of Medicine, Peking Union Medical College.

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THE PLATELETS IN TYPHUS FEVER

Reports of the behavior of the blood platelets during typhus fever are scarce. It therefore seemed of value to make a series of observations on patients with typhus fever to ascertain whether the platelets respond in the usual way to an acute febrile disease or in a manner peculiar to typhus fever. The present paper states the results of observations on the fluctuation of the number of the platelets during typhus fever. Experimental studies regarding the relationship between the platelets and the virus of typhus fever are also described.

Method.—The platelets were counted by the direct method. A modification of Thomsen's technic, described in detail elsewhere,⁷ was used. Briefly, the method comprised the following procedures: Blood was drawn from a vein into a small syringe containing citrate solution. The citrated blood was allowed to sediment. The sedimentation permitted the red cells to settle, while the platelets remained in homogeneous suspension in the supernatant plasma. The platelet suspension was then suitably diluted with physiologic sodium chloride solution containing a trace of formaldehyde; it was then placed on the hemocytometer slide and counted. By calculation, the number of platelets per cubic millimeter of blood could be reliably estimated. Normal human blood, according to this method, contained approximately 350,000 platelets per cubic millimeter.

Platelet Counts.—The clinical material used in this study was obtained at the time of an outbreak of an epidemic of typhus fever among Chinese military prisoners during the winter of 1928. Thirteen patients were studied. Their cases were uncomplicated and of moderate severity. It was not always possible to ascertain precisely the date of onset of the disease in each case; most of the patients, however, came under observation on about the fifth day of the illness. The average duration of the febrile period was fifteen days. Platelet counts were made, as a rule, every other day during the early period and at longer intervals during convalescence.

The curves made by charting the various platelet counts were, in most cases, similar in form. As in other acute febrile diseases of comparatively short duration, a thrombopenia occurred during the febrile period, followed, during convalescence, by a rise toward the normal level. In three cases, the number exceeded the normal level, that is, a transient thrombocytosis occurred. Chart 1 shows an example of this type of curve.

The thrombopenia was usually more pronounced and the subsequent increase in the number during convalescence was markedly delayed in typhus fever in contrast with the behavior of the platelets during lobar pneumonia.⁷ In five patients, the number never attained the normal level during observation over a period of from twenty-six to thirty-seven days. In five, after the number had increased slightly following the initial thrombopenia, it again fell to a level of about 200,000, at which it remained until the patients left the hospital. A curve of this nature is illustrated in chart 2. An unexplained peculiarity was observed in nearly all the cases and is illustrated in charts 1 and 2. It was the tendency toward a second phase of thrombopenia following the initial increase in number.

The lowest count observed, 8,000 per cubic millimeter, occurred in a patient on the seventh day of the disease. In this instance, the platelet suspension (after

7. Reimann, H. A.: J. Exper. Med. 40:553, 1924.

sedimentation of the blood) was placed directly on the slide, without dilution, and the platelets counted. In this patient, the number subsequently increased slowly and reached only 168,000 per cubic millimeter on the twenty-first day of convalescence.

Comment.—In general, it may be stated that contrary to the observations made by Pletnew,⁸ no distinct relationship between the severity

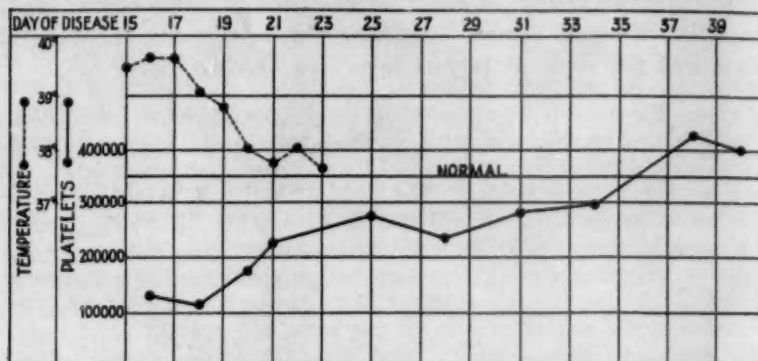


Chart 1.—The blood platelet curve in a case of typhus fever, showing thrombopenia in the febrile period and a transient thrombocytosis during convalescence.

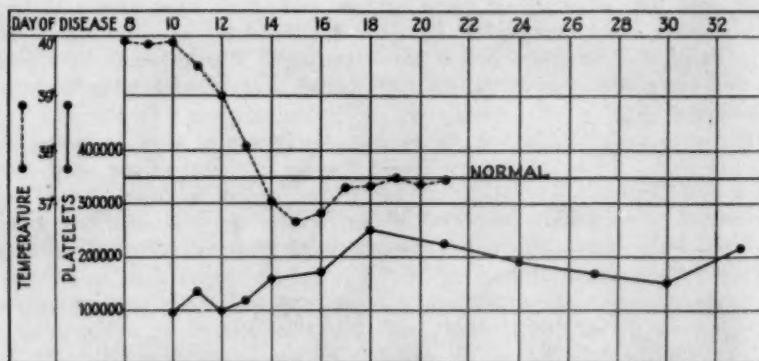


Chart 2.—The blood platelet curve in a case of typhus fever. The curve shows a prolonged thrombopenia.

of the illness and the degree of the thrombopenia was recognized. Neither did there seem to be any association between the presence and the severity of the exanthem and the number of the platelets. Epistaxis and a tendency to bleed from the gums was observed only in the patient showing the extremely low count.

8. Pletnew, D.: *Ztschr. f. klin. Med.* **93**:285, 1922.

THE RELATIONSHIP BETWEEN THE VIRUS AND THE PLATELETS

An experimental study was made to determine whether or not the virus (*Rickettsia prowazeki*) was free in the blood stream or contained in the platelets. Blood from patients with typhus fever and from experimentally infected guinea-pigs was used.

Methods.—A stock strain of the virus of typhus fever in animals was started by the injection of 5 cc. of patients' blood, taken on the eleventh day of illness, into the peritoneal cavity of a guinea-pig. Thereafter, for propagating the virus, the method of Weil and Breinl⁹ was adopted. Briefly, the technic was as follows: From five to ten days after inoculation with the typhus fever virus, the guinea-pigs developed a typical fever, which lasted from seven to nine days. On the fourth day of the fever, an animal was killed, and the brain was removed aseptically and emulsified in 20 cc. of physiologic solution of sodium chloride; 1 cc. of this emulsion was used for further inoculation. All animals were inoculated intraperitoneally. On several occasions during the passages of the virus, sections were made of a portion of the brain used for the transfer, and the characteristic histologic lesions of typhus fever were found. Tests of immunity to verify the specificity of the fever were also made in those cases in which this procedure was indicated, by allowing a period of at least two months to elapse from the time the animal recovered from the first fever before reinoculating it with known typhus virus. The animal was considered immune if fever failed to develop within thirty days after the reinoculation.

Platelets from human blood were obtained by running from 20 to 50 cc. of blood into an equal amount of a 10 per cent solution of sodium citrate in physiologic sodium chloride solution. The mixture was centrifugated at slow speed for ten minutes. The erythrocytes and leukocytes thus formed a sediment, leaving the platelets in suspension in the supernatant plasma. The platelet suspension was then centrifugated at 3,300 revolutions per minute for one hour. The clear supernatant fluid was removed, and the platelets were resuspended in a small amount of physiologic sodium chloride solution. A sediment of cells was not obtained by further centrifugation of the clear plasma.

Platelets were obtained from guinea-pigs in a similar manner. The blood was withdrawn from the heart and immediately mixed with the citrate solution.

Experiments with Human Blood.—Blood specimens from thirteen patients were treated in the manner described. As a rule, 50 cc. was withdrawn, and the platelets obtained from this amount was resuspended in 1 cc. of physiologic solution of sodium chloride. Portions of this suspension and 10 cc. amounts of the diluted clear plasma were then injected, respectively, into guinea-pigs in two separate series. Several of the animals receiving the plasma died shortly after the injections.

Of the ten animals surviving the injection of the plasma, seven showed the characteristic typhus fever reaction, and proved immune to subsequent reinoculation. The remaining three animals failed to develop fever following the injection of the plasma, but after reinjection of known virus two months later, they developed typhus fever.

All but two of the thirteen guinea-pigs inoculated with the platelets developed typical typhus fever. One of the two died before the reinoculation; the other developed typical typhus fever after reinoculation with virus from the brain three months later. Apparently, the percentage of animals successfully infected was about the same whether the platelets or the clear cell-free plasma was used.

9. Weil, E., and Breinl, F.: J. Infect. Dis. **33**:60, 1923.

Another experiment was then made by allowing 10 cc. of blood from a patient with typhus fever to clot and then separating the serum by centrifugation at high speed for twenty minutes. The clear cell-free serum was divided into three 1.5 cc. lots, and these were injected intraperitoneally into three guinea-pigs. Two of the three animals developed typical typhus fever ten days later. The third was apparently not infected.

Comment.—The experiments with human blood indicate that the virus of typhus fever exists free in the plasma and is not necessarily associated with the formed elements of the blood.

Experiments with Guinea-Pig Blood.—The methods employed in the experiments with human blood were used. Blood to the amount of 20 cc. was obtained from a large guinea-pig on the fourth day of experimental typhus fever. One half of the blood was received into an equal amount of citrate solution, and centrifugated as usual, so that the platelets were suspended in the supernatant plasma.

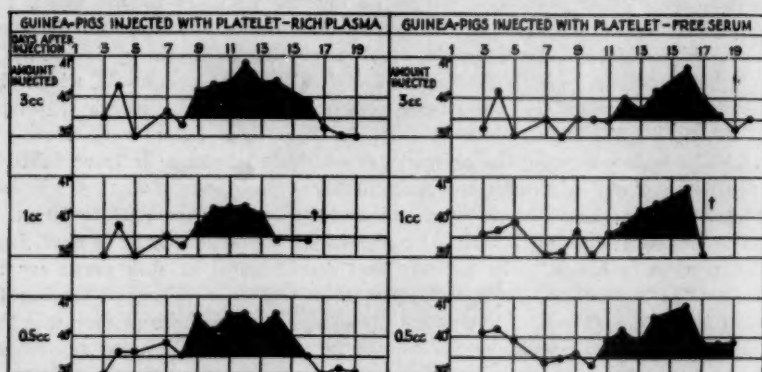


Chart 3.—The temperature reactions of two groups of guinea-pigs one of which had received injections of platelet-rich typhus fever plasma and the other, injections of platelet-free serum. Typhus fever of similar severity was induced in each group. † indicates death.

The other half of the blood was allowed to clot. Three normal guinea-pigs were inoculated with 0.5 cc., 1 cc. and 3 cc. of the platelet-plasma suspension, respectively, and three were inoculated with corresponding amounts of the platelet-free serum derived from the same sample of blood. The results are shown in chart 3.

Comment.—It is evident from the reactions of the animals that both the platelet-rich plasma and the platelet-free serum induced typhus fever of similar severity.

SUMMARY AND CONCLUSION

From the results of observations and experiments in this study, evidence is presented against the view that the blood platelets contain the virus of typhus fever or that the two factors are closely associated. The fluctuation in the number of blood platelets in patients during typhus fever, though similar to that observed in other febrile diseases,

is somewhat peculiar as compared with the changes usually observed in other acute febrile diseases. The thrombopenia is usually more pronounced, the subsequent return to the normal number is retarded and a tendency to a secondary thrombopenia usually occurs. This unusual behavior may be attributed to two factors: 1. Typhus fever is usually of longer duration than some of the diseases in which the platelet count has been followed (e. g., lobar pneumonia). 2. The lesions of the disease chiefly affect the blood vessels. It can scarcely be admitted that the variations in the number of platelets during typhus fever indicate any connection between the platelets and the virus of the disease.

Experimentally, the platelet-free plasma and serum produced typical typhus fever reactions in guinea-pigs about as regularly as did the platelet suspension. The specificity of the reactions was repeatedly verified by tests for immunity, by transference of the disease to fresh animals and by examination of sections of the brain. From these observations, it would seem that the virus exists free in the blood stream, although attempts to demonstrate *Rickettsia prowazeki* in this study by staining were not successful. It is possible that a similar specific gravity of the platelets and the virus may account for the concentration of the virus in the sediment of platelets after centrifugation, which several observers have reported.

We conclude, therefore, that an association does not exist between the blood platelets and the virus of typhus fever, and that the latter exists free in the blood stream.

EXPERIMENTAL STUDIES ON THE RETICULO- ENDOTHELIAL SYSTEM

IV. EFFECT OF HORMONES ON THE ELIMINATION OF BILIRUBIN *

M. A. GOLDZIEHER, M.D.

AND

M. LURIE, M.D.

BROOKLYN

The work of Mann and Magath¹ and others has drawn attention to the rôle of the reticulo-endothelial cells in the production of bilirubin. On the other hand, Melchior, Rosenthal and their co-workers² still maintain that the main organ in the production of bilirubin is the liver. They do not exclude, however, the reticulo-endothelial cells from the elements which are capable of transforming hemoglobin derivatives into bile pigment.

Experimental work in our laboratory³ has shown that the function of the reticulo-endothelial cells can be stimulated by hormones. Others (Leites and Riabov⁴ and Jaffe⁵) have confirmed this fact.

The following studies have been made to determine whether the elimination of bilirubin can be influenced by various hormones if the latter are given simultaneously with the injection of bilirubin.

Blood serum was obtained by centrifugation and a double volume of acetone was added. After a second centrifugation, a clear solution was obtained, which was a faint yellow. This solution was compared colorimetrically with a standard solution of potassium bichromate.

EXPERIMENTAL DATA

Experiments on rabbits showed that there is only a small amount of bilirubin present in the blood normally, and as there is little, if any, variation in this amount it was decided to disregard the physiologic bilirubin of the blood serum in the experiments.

One centigram of pure bilirubin dissolved in slightly alkaline water was injected into the vein of an ear, and blood was examined with the

* Submitted for publication, Nov. 19, 1928.

* From the Department of Laboratories, United Israel Zion Hospital, Brooklyn.

1. Mann and Magath: *Tr. Sec. Path. & Physiol.*, A. M. A., p. 29, 1921.

2. Melchior, Rosenthal and Licht: *Arch. f. exper. Path. u. Pharmacol.* **4**:28, 1922; *Klin. Wchnschr.* **1**:2265, 1922.

3. Goldzieher, M. A., and Hirschhorn, L.: *Reticulo-Endothelial System: Influence of Hormones*, *Arch. Path. & Lab. Med.* **4**:958 (Dec.) 1927.

4. Leites, S., and Riabov, A.: *Ztschr. f. d. ges. exper. Med.* **59**:709, 1928.

5. Jaffe: *Ztschr. f. d. ges. exper. Med.* **62**:538, 1928.

colorimeter at intervals. The concentration of the bilirubin in the blood was figured in the following manner:

Because of the size of our animals, the quantity of blood in a rabbit was put at 100 cc., in conformity with the generally accepted data. Thus, 1 cg. of injected bilirubin was diluted 10,000 times. The addition of a double volume of acetone to the serum raised the dilution to 1:30,000.

Repeated experiments on ten animals showed that the rate of elimination of the bilirubin injected remained the same in the same animal. Variations were negligible and ranged from 0 to 6 per cent. On the other hand, if the time of elimination in the different animals was compared, considerable variations could be established. Fifteen minutes after the injection the bilirubin was either entirely eliminated or only a small part was retained in some animals. In other animals, if the test was also made after fifteen minutes, from 15 to 25 per cent was found to be still present, and in a third group the retention at the end of fifteen minutes was still from 50 to 60 per cent of the quantity injected. In the later stages, the bilirubin disappeared gradually from the blood of all the animals and in two or three hours even the slowly eliminating animals were practically free from it.

Because of the different speeds of elimination, the animals can be divided into three groups: (1) quickly eliminating animals, which eliminated from 100 to 90 per cent within fifteen minutes; (2) animals eliminating from 85 to 75 per cent in the standard time of fifteen minutes; (3) slowly eliminating animals which eliminated less than 75 per cent in fifteen minutes.

We had thirteen animals in the first, seven in the second and four in the third group. In these twenty-four animals, the effect of hormones was tried on the elimination of bilirubin.

The hormones used were epinephrine, solution of pituitary, a thyroid preparation, insulin and interrenin⁶ (the hormone of the supra-renal cortex. The doses given were: epinephrine, 1 cc. of 1:4,000 solution; solution of pituitary, 1 cc. of 1:10 solution; a thyroid preparation, 0.5 cc. of the stock solution; insulin, $\frac{1}{2}$ unit; interrenin, 0.5 cc. of 1:20 stock solution.

It seems that three hormones, namely, epinephrine, solution of pituitary and insulin, have a similar effect on the quickly eliminating animals, as only from 57.5 to 67 per cent of the bilirubin was eliminated, instead of the 96 per cent in the previous control experiments. The effect of these hormones is less marked in the intermediate group. Thus, epinephrine seems to accelerate the elimination slightly (from 81 to 86 per cent), whereas solution of pituitary and insulin accelerated from 80 to 90 and 95 per cent, respectively.

6. Goldzieher, M. A.: *Klin. Wehnschr.* 7:1124 (June) 1928; *The Adrenals*, New York, The Macmillan Company, 1928.

In the group of slowly eliminating animals, the effect is pronounced and just opposite to that in the first group. The elimination is accelerated by epinephrine, solution of pituitary and insulin from 54 to 90, 88 and 85 per cent, respectively. The two other hormones are decidedly different in their effect. Interrenin is exceedingly effective with the slowly eliminating animals, as the elimination is accelerated from 53 to 93 per cent. In the quickly eliminating group, as well as in the intermediate group, the effect of interrenin is practically nil. In marked contradistinction to all the other hormones, a thyroid preparation has practically no effect on elimination, and this holds true for all three groups of animals.

The next step was to determine whether the formation of bilirubin from laked blood could also be influenced by the same hormones. To this end a series of white rats received intravenous injections of laked blood of a sheep; 3 cc. of blood was injected, and twenty-one hours later samples of blood were examined for the presence of bilirubin. It seems that the rate of the formation of bilirubin in the rats injected with hemoglobin varies individually. Taking an average figure, it appears that a normal rat produces, in the standard time of twenty-one hours after injection, 1.75 units of bilirubin. The differences downward and upward range between 1.4 and 2.2 units.

Rats into which were injected laked blood were given hormones, the hormones being injected twice on the day that the blood was injected and again on the morning of the following day. The sample of blood for estimating bilirubin was taken one hour after the last injection.

Normal animals that had received a solution of pituitary, epinephrine or a thyroid preparation showed an average figure of 1.7 and 1.9, respectively, which does not differ materially from the normal average. The variations were distributed over a far greater range, namely, in the injections of a solution of pituitary, from 0.5 to 2.5; in the experiments with epinephrine the results varied from 1 to 3, and in the thyroid group from 0.5 to 3.5.

More conspicuous differences were brought out in the experiments with insulin and interrenin, as averages were 1.1 and 2.7, respectively. In other words, less bilirubin was found after the administration of insulin and considerably more after interrenin had been given. The individual variations in the experiments with insulin ranged from 0.2 to 2, while in the interrenin group, the figures ranged from 1.25 to 5.

The results of these experiments are difficult to interpret, as they represent most probably the effect of the hormones on both the formation and the elimination of bilirubin. In view of the fact that the specimens of blood were taken one hour after the last injection of hormones, it seems probable that the excessive or decreased production of bilirubin

accounts for the different results. At least the first series seems to show that the effect of hormones on elimination subsides within an hour.

In referring to previous experiments, as well as to the observations of others, one may recall the marked stimulating or inhibiting effect of hormones on the reticulo-endothelial system. We are inclined, therefore, to suggest that the results of the second series indicate an effect of hormones on the reticulo-endothelial system in the production of bilirubin from hemoglobin.

In a third series of experiments, the attempt was made to study whether the hormonal interference with the reticulo-endothelial cells is also effective if jaundice was due to some hemolytic poison. In this experiment nine rabbits were injected repeatedly with 5 cc. of a 1:500 solution of phenylhydrazine. The injections were given subcutaneously on three consecutive days, once a day, and on the fourth day a sample of blood was taken for examination. The quantity of bilirubin demonstrated in this sample was low in spite of the development of marked anemia. The animals were left alone for two weeks until they seemed to recuperate, and then the injection of phenylhydrazine was repeated with simultaneous injections of hormones. The results obtained were not satisfactory, as the quantities of bilirubin in both the control experiments and the hormone experiments were too small to allow of comparison. It is possible that the same experiment might yield more valuable results if another hemotoxin was chosen or a more suitable procedure used.

COMMENT

The experiments have shown that the elimination of bilirubin injected into animals is subject to variations which seem to depend on a constitutional factor. Thus, the animals belong to two groups, which may be called the quickly and the slowly eliminating groups. Other animals range in between the two main groups.

We do not know the factors which account for the constitutional differences in the elimination of bilirubin; yet the following explanation might be suggested: Our experiments have established a stimulating or inhibiting effect of hormones on the elimination of bilirubin. We also claim that such an effect of hormones is due to the interference with the function of the reticulo-endothelial cells. Hence, we should conclude that physiologic elimination of bilirubin is also regulated by the action of the endocrine glands on the reticulo-endothelial system and perhaps also on the liver. The constitutional differences between the various animals would express a different state of the endocrine balance, which is upset by the additional administration of hormones, with the result that retardation occurs in the quickly eliminating group and acceleration in the slowly eliminating group. It is a prevailing con-

ception that the hormones can be grouped into antagonists and synergists such as, for instance, epinephrine on the one hand and insulin on the other. Such antagonism between the various hormones is not demonstrable in the effect of the substances on the function of the reticulo-endothelial system.

The evidence offered that hormones also influence the production of bilirubin is less unequivocal; yet it seems that there are changes of bilirubin formation due to the effect of injected hormones. This would suggest that the endocrine glands exert influence on this phase of intermediary metabolism and that endocrine disturbances may play a rôle in certain types of jaundice.

That hormones have a certain influence on the course of jaundice has been proved before; at least, so far as insulin is concerned. It has been shown by Echauz,⁷ Bamberger⁸ and others that the administration of insulin is instrumental in decreasing jaundice as to both its intensity and its duration. Insulin therapy in acute hepatic conditions, of course, has been introduced on the basis of different considerations. When injected simultaneously with dextrose, insulin was supposed to alleviate the disturbances of the carbohydrate metabolism, but at the same time its effect on jaundice became visible.

Our results show that insulin was the most active hormone in decreasing the formation of bilirubin and seem to bear out the empiric clinical observations.

CONCLUSIONS

Constitutional differences in the rate of the elimination of bilirubin are established in normal animals. Injections of hormones influence the rate of the elimination of bilirubin, and hormones seem to influence the formation of bilirubin.

7. Echauz, F.: *Arch. de med. cir. y espec.* **26**:558 (April) 1927.

8. Bamberger, J.: *Deutsche med. Wchnschr.* **53**:1690 (Sept.) 1927.

General Review

MULTINUCLEATED GIANT CELLS

WITH PARTICULAR REFERENCE TO THE FOREIGN
BODY GIANT CELL *

SAMUEL R. HAYTHORN, M.D.

PITTSBURGH

Introduction

Varieties of Multinucleated Giant Cells

- Langhans' Giant Cell
- The Foreign Body Giant Cell
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- Syncytial Giant Cells
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Fate of Giant Cells

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* From the William H. Singer Memorial Research Laboratory of the Allegheny General Hospital.

Occurrence of Giant Cells

- In Simple Granulation Tissue
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- In Tuberculosis
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Critical Conclusions

INTRODUCTION

Large multinucleated giant cells are widely distributed in the tissues, in the physiologic and pathologic processes of which they play an important rôle. They appear to fall into two fairly well defined groups. In one group are the multinuclear tissue type cells, arising by atypical nuclear division, and associated with proliferative processes generally. In the other group are one or more varieties of large, round or oval, multinucleated cells, associated with inflammatory reactions, and found about insoluble substances and foreign bodies. It is with the latter group that this review is chiefly concerned.

Faber⁹⁷ credited Johannes Müller,²⁷¹ who published a treatise on tumors in 1838, with the first description of foreign body giant cells. Robin³⁰⁵ noted their presence in bone tissues in 1849. Paget²⁷⁰ discussed them in his lectures in 1853 and Virchow²⁵⁰ devoted considerable attention to them in his *Cellularpathologie*, published in 1858. Langhans wrote an exhaustive thesis on giant cells in 1868; and his comprehensive interpretation of their origin, nature and distribution was justly recognized by the application of the name "Langhans' giant cell" to the cell in question. Following the article by Langhans, the interest in giant cells developed rapidly, and a great many papers appeared, dealing chiefly with their origin, significance, diagnostic importance, similarities and differences. Between 1870 and 1900, there occurred an enormous number of contributions. Between 1900 and 1920, a much smaller number were forthcoming, although the interpretation of the nature of these cells seems to have undergone its greatest development during this time. Since 1920, the advent of vital staining and vitally stained tissue cultures seems to have revived interest in them, and many valuable contributions have appeared recently. In short, the literature on giant cells parallels the entire history of the development of microscopic anatomy and pathology, including, as it does, the days of the blastema

theory with its "mütterzellen" and the present day period of the development of lesions in vitro by vitally stained cells under the influence of vitally stained bacteria as irritants. It is my hope, in this review, to bring out most of the views about giant cells, and to incorporate a sufficient number of articles to support the statements; the literature is so extensive and so involved that a claim of completeness in any sense may not be made.

VARIETIES OF MULTINUCLEATED CELLS

The early observers discovered the presence of giant cells in many widely varying lesions and assumed that they would be found to differ more or less with the nature of the disease, with the type of tissue involved and perhaps even with the species of animal under examination. Robin³⁰⁵ and Kölliker¹⁹⁶ found them in bone; Virchow³⁰⁰ found and classed together similar structures in tubercles, in muscles undergoing repair and in nerve tissues. Weigert³⁷¹ stated that tubercle giant cells with peripherally arranged nuclei were to be found not uncommonly in sarcomas, and that, conversely, sarcoma giant cells with centrally placed nuclei were to be found in tuberculosis. When it is recalled, in addition to the morphologic differences and the unusual distribution of multinucleate cells, that histologic technic was in its infancy, it is not surprising that great confusion arose and that some writers spoke of the cells as separate entities, while others classed them all together as a single type of cell. The confusion, for the most part, no longer exists, though there is at present no uniformity of opinion about the various types of tumor giant cells. It seems advisable to make a preliminary discussion of the various kinds of giant cells as they have been classified, namely, the Langhans giant cell of tuberculosis, the foreign body giant cell (including those found in tumors and granulomas), the osteoclast, the megakaryocyte, the muscle giant cell, the giant cells of nerve tissues, the true epithelial syncytia and the various true tumor giant cells.

Langhans' Giant Cell.—Langhans,²¹¹ in 1868, appears to have been the first to devote an entire paper to the discussion of giant cells. He reviewed the literature then in existence and referred to Rokitsansky³⁰⁷ and his theory of "mütterzellen"; to Virchow,³⁵⁰ who first described the early tubercles of the peritoneum and omentum; to Robin³⁰⁵ and his "myeloplaxes"; to E. Wegner,³⁶⁸ who described giant cells in tubercles of the liver; to Busch,⁶¹ who found them in the chorioid; to Bredichin,⁴⁸ who thought that they were formed in bone by the flowing together of several cells, and to Rindfleisch,³⁰³ who thought that they came from endothelium of the lymph spaces. He also mentioned Buhl,⁵⁵ Deichler,⁶¹ Colberg⁷⁰ and Manz²⁴⁶ as having described them.

Much of Langhans' work was done on fresh tissues either teased out or crushed and examined in salt solution, serum or glycerin, or in

chromic or acetic acids. He usually made his preparations from fine miliary tubercles of the pleura or peritoneum. He demonstrated the cells, however, in practically every tissue of the body. He felt that they were specific structures and were similar in nature regardless of their tissue source. The question arose in his mind as to whether or not they actually were cells, and because of the action of chromic acid on his fresh preparations, he decided that they were. He found that they varied greatly in shape, size and the number of nuclei. Some were round, some oval, some elongated or sausage shaped, some elliptical, some irregular and some more or less stellate. Some were sharply defined, some had attached mantels of adherent spindle cells and others were less well demarcated. He noted that, in size, they varied from small cells with from two to four nuclei, to large cells measuring from 0.2 to 0.3 mm. in diameter and having from thirty to 100 or more nuclei. The nuclei were characteristic, usually round or oval, with sharp outlines and vacuolated centers, and generally contained nucleoli. The arrangement of the nuclei was, for the most part, characteristic; it was peripheral, with the long axis of the nucleus at right angles to the cell wall, but this did not hold throughout. Some of the cells had the nuclei grouped in a bipolar arrangement, and some had them diffusely distributed throughout the cell. The protoplasm of the giant cell was pale, homogeneous or finely granular, with the center usually clear. Sometimes, the outlines of a fine fibrillar net work could be made out in the protoplasm. In teased preparations, the cells became cloudy, and cleared when acetic acid was added.

Langhans raised the question whether the cell arose from its own action or was derived from the surrounding tissues. He thought that the giant cells originated from the surrounding cells and that the spindle cells played the principal part. He advanced several arguments for his view: The nuclei were similar to those of the surrounding cells and were situated, as a rule, in the periphery of the cell. Sometimes the surrounding spindle cells were flattened out like plates on the sides of the giant cells, and sometimes they extended outward from the giant cells to join with the neighboring cell groups; this observation suggested that the cells were either flowing into the giant cell or being cast off from it. Finally, he thought the included fibrillar network resembled the fibrillar arrangements of the surrounding tissues.

He introduced the discussion regarding nuclear division of one cell as opposed to the fusion of several cells to form the giant cell. Although fusion had not been demonstrated in man, he considered it possible.

Langhans' description of the giant cell of tuberculosis is classic and complete, and the synonymous use of "tubercle giant cell" and "Langhans' giant cell" would be justified, if it were not that the description

is just as accurate for any foreign body giant cell as it is for that of tuberculosis. While the term "Langhans' cell" is usually applied only to those cells with peripheral (wandständige) nuclei, Langhans also described the forms with bipolar and diffuse distribution of nuclei, so that it is probably correct to apply the name "Langhans' cell" to any foreign body giant cell.

Further discussion of the tubercle giant cell will be taken up under the head, "Occurrence in Tuberculosis."

The Foreign Body Giant Cell.—The term "foreign body giant cell" has been applied to a type of multinucleated cell which is identical with Langhans' cell in structure and appearance, and which soon appears in the vicinity of any foreign or insoluble substance in the tissues that is too large to be taken up by a single cell.

Mallory^{242a} described the foreign body giant cell as follows:

When an endothelial leukocyte finds difficulty in dissolving a substance, as, for instance, lime or certain fat products, it frequently fuses with other endothelial leukocytes to form a multinucleated mass of cytoplasm, commonly termed a foreign body giant cell. If the foreign body is too large for one leukocyte to incorporate (cholesterin crystals, hair, etc.), one or more giant cells are formed which surround it or cluster themselves upon its surface.

The present consensus of opinion appears to be that the only difference between Langhans' giant cells of tuberculosis and foreign body giant cells is one of environment.

The misunderstanding about the nature of the giant cell of tuberculosis and the foreign body giant cell, as encountered in other conditions, arose chiefly because of the locations of the nuclei. In tuberculosis, the peripheral, bipolar and horse shoe arrangements are more commonly found; while about inert foreign substances the nuclei tend to be diffusely or centrally placed.

Metschnikoff²⁰⁰ and later Adami¹ demonstrated that when inert foreign particles were introduced into the body cavities of *Astropecten* and other lower forms, multinucleated plasmodia were found about them. Ziegler,³⁸⁸ with some ingenious experiments later to be discussed, obtained foreign body giant cells about glass platelets, and interpreted them as being identical with those found in tuberculosis.

Köckel¹⁹⁵ maintained many years ago that Langhans' cell in tuberculosis was not characteristic, but was the accidental presence of a foreign body giant cell in an unusual environment. Krückmann²⁰⁴ undertook to determine the identity of giant cells as they were encountered in tuberculosis, about parasites and foreign substances and in sarcomatous and epithelial tumors. While he believed that the giant cells could arise from several different kinds of mononuclear cells, he concluded that microscopic means were not at hand by which they could

be distinguished. Hektoen ¹⁴⁸ and recently Maximow ²⁵⁸ stated definitely that Langhans' cell is merely a foreign body giant cell occurring in tuberculosis.

On the other hand, Jacobson ¹⁶⁸ published an outline for the differential diagnosis of six kinds of giant cells, including those of the tubercle, and Lubarsch ²²⁸ said that the picture in tuberculosis is so characteristic that one speaks of the tubercle giant cell to the exclusion of all other forms.

Burgess demonstrated that typical Langhans' giant cells could be formed experimentally about the soaps and salts extracted from foci of caseation.

The Osteoclast.—Large multinucleated giant cells are present in practically all conditions in which bone is formed or resorbed. They appear during embryonic development, and are increasing during repair after fractures and in most inflammatory and neoplastic diseases. These cells are the osteoclasts of Kölliker ¹⁹⁷ (1873). They measure from 40 to 90 microns long, and from 30 to 40 microns broad. In normal bone, they are found in Howship's lacunas, either singly or in groups, and are active in all conditions in which bony resorption is a part of the process. Kölliker thought that they arose from osteoblasts by repeated nuclear division. In Stöhr's Textbook of Histology ³⁸⁶ the statement is made that they do not appear to be due to a fusion of cells, and that they have nothing in common, except their large size, with the giant cells of the bone marrow (the megakaryocytes of Howell ¹⁶⁴), but are found along the surface of the bone or in the lacunas. According to Stöhr, satisfactory evidence has not been found that osteoclasts are the active cause of bone destruction; they appear to be degenerating cells, brought to that pass by the same conditions which lead to bony dissolution. This last statement, however, is not in accord with the majority of expressed views about osteoclasts.

Kölliker studied them in fresh and fixed preparations. In the fresh state they were indefinite in outline and degenerated quickly. He described them in the long and the membranous bones. Rustizky ³¹¹ studied these cells in bony lesions of various kinds, including those gathered in a layer against bony margins, those in sarcomas and myelomas, those found in granulomas, and those found in the healing of fractures and old calluses, as well as those around hemorrhages and deposits of hyaline fibrin. He concluded that they were giant cells which were not specific for the lesions in which they occurred, but were the same throughout. He connected them with bony resorption and said they all contained calcium granules. G. Wegner ³⁰⁹ identified the "plaques a noyaux multiples," later known as the "myeloplaxen" of Robin, with these giant cells. He found them in the periosteum and

bone marrow of several patients whose cases were associated with resorptive lesions. He thought they came from the proliferation of cells in the vessel walls, and that the nuclei increased through nuclear proliferation of a single cell. As evidence, he pointed out the irregular increase in the number of nuclei, and the constant central grouping of nuclei in the younger cells. Bredichin,⁴⁸ quoted by Langhans, thought that osteoclasts were foreign body giant cells, and were formed by the fusion of like cells. Virchow²⁵⁰ and Rindfleisch²⁰³ believed that foreign body giant cells and the osteoclasts were the same. Among the more recent writers on this subject, Mallory^{242b} stated that the osteoclast is a foreign body giant cell formed by the fusion of endothelial cells. MacCallum^{233a} used "great phagocytic cells" of bone and "osteoclasts" synonymously. Ewing apparently did not consider them identical, for he discussed giant cell tumors as osteoclastomas^{26d} and as being in a different group from sarcomas containing foreign body giant cells. Marchand^{256b} stated that osteoclasts are nothing else but a kind of foreign body giant cell with a special function to perform.

Most modern writers group the Langhans cell of tuberculosis, the foreign body giant cell about inert substances and in miscellaneous granulomas and the osteoclasts together as one type of cell, which forms in response to the stimulus of some foreign substance, and which varies morphologically only with local environmental influences.

The Megakaryocyte.—In addition to the osteoclasts of Kölliker, there is a second type of giant cell present in bone marrow which is known as the "megakaryocyte." It is not a true multinuclear cell, but has a large, single multilobulated nucleus which may be crown shaped, irregularly lobulated or polymorphic, and which, according to Bunting,⁵⁷ may be made up of several vacuolated nuclei bound together. About the nucleus is a zone of coarsely granular protoplasm, and outside it a relatively clear or finely granular area (Schridde³²⁴). Jordan¹⁷⁵ found that the cytoplasm contained mitochondria and a Golgi apparatus. These cells multiply by mitosis (Arnold⁸). They phagocytose red blood corpuscles (Piersol²⁹¹). Wright³⁸⁴ proved that they give rise to blood platelets through the snaring off of pseudopodia from their protoplasm.

In the German literature prior to 1890, these cells were generally discussed collectively under the name "Knochen Riesenzellen." Marchand^{253b} credited M. Heidenhain¹⁴⁶ (quoted by Schmaus and Albrecht,³¹⁷ 1892) with the separation of the giant cells of the bone marrow into two groups: the "Knochenmarkzellen," or "Riesenkernzellen," and the "Riesenzellen of Kölliker," or osteoclasts. Two years earlier, Howell¹⁸⁴ had differentiated these cells and separated them into the two classes. Howell appears to have been the first to apply the term "megakaryocyte." As Marchand pointed out, they have nothing to do with each other.

With modern technical methods, megakaryocytes are readily excluded from the group of foreign body giant cells, and need not be discussed further.

The Giant Cells of the Muscles.—Two kinds of giant cells have been described as occurring in striped muscle: the multinucleated forms of the rhabdomyosarcoma, which are actually atypical muscle cells (Ribbert³⁰¹), and about the nature of which there is no doubt, and the repair clubs of striped muscles, which have frequently been mistaken for foreign body cells. Virchow³⁵¹ mentioned the resemblance of the latter type to myeloplaxes, and Marchand^{358a} included them among his sources of foreign body giant cells. Lejars²¹⁰ described tuberculosis of muscle with the formation of Langhans' cells from the striped fibers. Mallory^{242c} explained the various appearances in injured striped muscle which simulated giant cells as follows:

When the whole muscle fiber is killed, it is not regenerated. When only a part of one of the fibers is destroyed, active regeneration of the part which has not undergone necrosis takes place from the part which remains uninjured. The intact nuclei undergo rapid direct division and each forms several dozen separate nuclei. The division of the nuclei may take place at the periphery of the cell, or in the center of its own axis. The new nuclei migrate to the periphery and the injured end of the muscle fiber. The partially dead muscle cell may be removed by polymorphonuclear leukocytes, and at other times endothelial leukocytes attack it and dissolve it, working from without inward. Mitoses in these endothelial leukocytes are not infrequent. Occasionally multinucleated cells result. More often they fuse to form foreign body giant cells. Sometimes the two processes go on at once, and render the picture difficult to interpret.

While muscle repair clubs may resemble foreign body giant cells, it is doubtful if they can take part in their formation in any capacity other than that of a foreign body which attracts them.

The Giant Cells of Nerve Tissues.—True foreign body giant cells, as well as other structures closely resembling them, may occur in nerve tissues. Completely degenerated ganglion cells without nuclei may be closely surrounded (neuronophagia) by phagocytes in such a way that the resemblance to giant cells with peripherally situated nuclei is simulated. Degenerated and inflamed nerves may also have their sheaths infiltrated with phagocytes so that they present a somewhat confusing picture. Indeed, true giant cells may be found in nerve trunks in leprosy and other granulomas. Areas of ischemic softening, hemorrhagic extravasations and other injury in the brain may contain many phagocytes, which may be single or multinucleated. The question has been raised as to whether the phagocytes in these areas are of mesoblastic or of glial origin. Alzheimer² divided glial cells into four groups, the second of which was made up of ameboid phagocytic forms which were active in phagocytosing injured brain substance. Giant cells are con-

stantly present in tuberculosis of the brain and in gummas, and it is accepted that these are ordinary foreign body giant cells. It seems therefore unnecessary to interpret the phagocytes of hemorrhagic areas in the brain as having a special origin from glial cells. According to Buzzard and Greenfield,⁶⁴ the question is not settled.

Syncytial Giant Cells.—In his series of articles on endothelial reactions, N. C. Foot¹⁰¹⁻¹⁰⁵ frequently makes references to the "large syncytia" of the tubercle. As one definition of syncytium is a group of cells without separating walls, this application of the term is, no doubt, correct. However, it has the disadvantage of using a name which was formerly applied to the multinucleated giant cells arising from the syncytial layer of chorion, called the "syncytial," or "placental," giant cells.

Placental giant cells are not related in any way to the foreign body giant cells, though they resemble them. They are tangential sections through the buds of syncytial cells on the villi of the developing placenta (Williams,²⁸⁰ Cullen⁷⁸). They were reported as occurring in the capillaries of the lung by Schmorl²²² in 1893, who considered their presence in that location as a part of the pathology of eclampsia. Luesden,²²¹ in 1895, also studied the pathologic changes of eclampsia, and found the giant cells, but stated that they occurred in normal pregnancies as well, and had nothing to do with eclampsia. Aschoff¹⁰ reported multinucleated syncytial cells embedded in the wall of the uterus in a specimen removed during cesarian section, and considered them to be placental giant cells squeezed off by uterine contraction. They are now generally recognized as a constant observation in pregnancy. The question of the source of these cells was for a long time in doubt. McCallum^{223c} pointed out that it has always been admitted that the Langhans layer originates from fetal ectoderm, but that the syncytial layer has been variously attributed to maternal epithelium, to maternal endothelium and to fetal ectoderm. Marchand²⁵¹ maintained that both layers came from fetal ectoderm, and Schlagenhauser²¹⁶ described these cells in chorion epithelioma of the testis, which completely ruled out the maternal sources and left fetal ectoderm as the only possibility.

Other epithelial syncytia are often mentioned interchangeably with giant cells. Aschoff described large masses of multinucleated syncytia in the liver, in lobular hypertrophy and repair of lobules of the liver and in cirrhosis and adenoma of the liver. I have recently seen two such cases, and agree with Aschoff that these masses, while true syncytia in liver cells, are in no way related to foreign body giant cells. Such masses commonly contain numerous large mitotic figures. Rowen and Mallory²¹⁰ reported a case of carcinoma of the liver in which the type cells were large syncytial cells.

These cells should not be confused with foreign body giant cells, to which they do not have any relation.

True Tumor Giant Cells.—Almost any rapidly growing tumor is likely to present multinucleate tumor cells. The sarcoma group is particularly apt to present such forms, and often contains ordinary foreign body giant cells as well. The true multinucleated tumor cells tend to differentiate like the mononuclear cells of the tissues from which they originate, and are characterized by their somewhat larger size, the number of their nuclei, the presence of mitoses, which may be atypical and of "giant" size, and the tendencies to contain hyperchromatic nuclear structures and multiple nucleoli. Further, they degenerate like the cells from which they come, and metastasize with other tumor cells. Save for the hyaline inclusions which are seen in some epithelial tumor cells and for fat and granular débris, they rarely contain phagocytosed particles. As characteristics which differentiate them from foreign body giant cells may be mentioned: their shape, which usually conforms in a general way with that of their fellows; the fewer nuclei, usually not more than six or eight, and the striking irregularities of their nuclei with reference to chromatin content and staining qualities. The foreign body cells usually are round or globular; tend to retract from the surrounding cells on fixation; have large numbers of typical nuclei, and often contain phagocytosed granules, particles of chromatin, entire cells and cellular débris.

A detailed discussion of the various types of tumor cells will be taken up in a later section.

Summary on Varieties of Giant Cells.—It is probable that the giant cells of inflammatory lesions, including tuberculosis and other chronic granulomas, those about foreign bodies and those in bones, known as osteoclasts, are variations of the so-called foreign body giant cell and are similar in origin and function. They will form the nucleus of the remainder of this discussion.

Megakaryocytes, muscle giant cells, syncytial giant cells and true tumor giant cells are specialized cells of distinct origins and separate functions, and are hereafter excluded from the general discussion. The various tumor cells will be considered as a part of the discussion of the occurrence of giant cells in tumors.

CELLS FROM WHICH GIANT CELLS HAVE BEEN REPORTED TO DEVELOP

In the earlier literature, the greatest confusion existed in regard to the types of cells from which giant cells could develop. Virchow⁸⁵² at first thought that they came exclusively from the cells of connective tissue, but later admitted the possibility of their origin from epithelium, from endothelium and, under certain conditions, from the cells of the

muscles and the nerves. Marchand's idea was that, since any large protoplasmic mass with more than one nucleus was classed as a giant cell, there must be many kinds. He believed that they differed greatly in significance, and that they could originate from various tissues, such as epithelial cells, muscle cells, connective tissue cells, fat cells, leukocytes and lining, or pavement, cells of the serous cavities and blood and lymph vessels. Few authors adhered entirely to a single source; and Arnold, who wrote four papers in support of the development from tubular epithelium, considered that they arose from endothelium⁶ in the lymph nodes.

Gradually the theories of origin from fixed endothelium and from epithelium, aside from the alveolar epithelium, have lost ground. Giant forms of the cells of muscle and nerve have been explained on a different basis, and megakaryocytes and placental syncytia have been recognized as unassociated structures, and so have been automatically removed from the possibilities. The arguments now rest on modifications of the Baumgarten²⁹ theory of origin from fixed connective tissue and proliferated endothelial elements and the theories of origin from wandering cells (Ziegler³⁸⁸ and Borrel^{43, 44}). In an attempt to present an idea of the sources of giant cells described in the literature, I have classified the views under several headings.

Origin of Giant Cells from Fixed Connective Tissues.—Baumgarten,²⁷⁻³⁰ E. Wegner,³⁶⁹ Lubimow,²³⁰ Brissaud and Toupe,⁵⁰ Billroth,³⁴ Kostenitsch and Wolkow,²⁰⁰ Straus³⁸⁸ and Klebs^{168, 169} were among the earlier writers who traced the formation of the tubercle to the cells of fixed connective tissue, and the tubercle giant cells, in turn, from the epithelioid cells. Some, as will later be shown, explained them on the basis of nuclear division; some by fusion of the involved cells, and some by degeneration and compression in such a way that the cell boundaries were lost. Rindfleisch³⁰⁴ studied the process of organization and encapsulation, and reported that the cells extending from the surrounding cells to the giant cells produced fibrils of true connective tissue. Falk,⁹⁸ in 1895, emphasized the fact that nearly all observers had given up the idea of giant cells coming from exudative cells, and had returned to the old idea of Virchow that giant cells come from the cells of fixed connective tissue. He himself shared in Baumgarten's idea that the tubercle came from fixed connective tissue which became infiltrated with wandering cells.

Origin of Giant Cells from Tubular Epithelium.—A fairly large number of pathologists were misled by the resemblance between giant cells with peripheral nuclei and hollow tubular structures, such as epithelial lined ducts and endothelial lined blood and lymph vessels, into postulating that giant cells were derived from such structures. Arnold,⁸ in several papers on the histogenesis of the tubercle, traced giant cells to epithelial ducts in every organ in which such structures occurred. In lymph nodes, endothelium, he believed, tended to undergo cornification into epithelioid cells and subsequently to change into giant cells. In

1880, he compared experimental tuberculosis of the liver in animals with his material obtained at autopsy, and concluded that giant cells came from bile ducts. He pointed out that giant cells and bile ducts were always found together in tuberculosis of the liver; and he believed that he was able to recognize every step in the transformation. He argued that the peripheral arrangement of nuclei, which had always been difficult to explain, became clear at once when tubular epithelial structures in tuberculous lesions were studied. In subsequent papers, Arnold^{4, 5} reiterated the statement that the origin of giant cells was from bile ducts, and also described their origin from epithelium of the seminiferous tubules in tuberculosis of the testis, from tubular epithelium in the kidney, and the possibility of their origin from any small epithelial duct or hollow epithelial canal in the body. While he discussed the origin of giant cells from sinus epithelioid cells in lymph nodes and from alveolar epithelium in pulmonary tuberculosis, Arnold most enthusiastically advocated their origin from tubular structures. Waldstein³⁵⁸ described "plates" of giant cells in the seminiferous tubules in tuberculosis of the testis. He found these cells fusing directly with the lining epithelium, and believed that the giant cells were epithelial outgrowths. Tizzoni and Gaule³⁴⁵ described the same giant cell pictures in the testis, but raised the question of their accidental occurrence in these sites. They did not deny that the cells came from the epithelium, but thought it more likely that they originated from the associated lymph channels. Borst,⁴⁵ Paltauf,²⁷⁷ Birch-Hirschfeld⁸⁷ and many others expressed themselves in favor of the origin of giant cells from tubular epithelium.

Origin of Giant Cells from Surface and Glandular Epithelium.—Aside from epithelial tumors, the origin of giant cells from surface epithelium has not been frequently reported. Askanazy¹⁶ traced them from the deeper layers of the skin after freezing the ears of rabbits with a mixture containing ether, and Weigert described "epithelial" giant cells in the margins of smallpox pustules. Krückmann,²⁰⁴ who made an extensive study of giant cells in experimental tuberculosis, in tuberculosis found at autopsy, and in tumors, thought that, while they usually arose from endothelium or fixed connective tissue, they could come from the fusion of displaced, squeezed or compressed degenerated epithelium. Krause²⁰² also studied the giant cells in epitheliomas and thought that those in the granulations about the tumor columns came from tumor epithelium. Borst⁴⁵ repeatedly asserted the epithelial nature of epithelial tumor giant cells. Krückmann included his series of tumors in dermoid cysts and sebaceous adenomas, and found giant cells which he attributed to epithelium. Zielonko³⁹⁰ reported them in chalazions and in the adenomas of the meibomian glands. I have seen them several times in the small xanthomas of the eyelids. Here the resemblance between the sebaceous glands filled with vacuolated sebaceous cells and the nests

of fat filled phagocytes, so-called "compound granule cells," is striking. It is easy to be mistaken, but I believe that the giant cells come from the compound granular cells.

Emanuel⁹⁰ believed that giant cells in the ovary could originate from lutein cells. It might be noted also that compound granular cells are common in ovarian inflammation, and that the resemblance between them and luteal cells is close enough to lead to error.

Origin of Giant Cells from Alveolar Epithelium.—In view of the lack of unity of opinion concerning the phagocytes of the lung and the application of the term alveolar epithelium to them, it seems best to consider them in a separate paragraph.

Formerly, it was pretty generally accepted that alveolar epithelium desquamated readily and took an active part in all the exudative lesions of the lung. The desquamated alveolar cell was described, and still is in many textbooks, as one of the first cells found in the exudate of pneumonia, and as the active phagocyte in the various dust diseases, the pigment phagocyte of chronic passive congestion, often called the "herz fehler zellen," and so on. There is no doubt that a phagocytic cell is active in all the processes mentioned, as well as in many other lesions, including the formation of miliary tubercles and of giant cells; but there appears to be a preponderance of evidence that the phagocyte is not an epithelial cell. With the conception of the epithelial origin of this cell, however, it was to be expected that tubercles and giant cells should be traced to "alveolar epithelium." Conspicuous among the group who described tubercles and giant cells as originating from the epithelium of the lung were: Arnold,⁷ Buhl,⁵⁶ Klein,¹⁹⁰ Friedlander,¹¹³ Beitzke³² and Herxheimer.¹⁵⁶

Mallory,²³⁹ in 1898, in his studies on typhoid fever, described the origin of the mononuclear phagocytes of the body from the walls of proliferating capillaries. The cells under the stimulus of the typhoid bacillus or its toxins underwent rapid proliferation and swelling, frequently showed numerous mitoses, and then wandered out into the surrounding tissues or were thrown off into the lumina of vessels. These cells were phagocytic and were called "endothelial leukocytes." While working in Mallory's laboratory, from 1908 to 1910, I learned his views, namely, that the endothelial cell was the active cell of the tubercle, and was the source of the phagocytes of the tissues and of the lung alveoli. The cells took up granules of pigment, tubercle bacilli and all sorts of foreign particles, and were thought to fuse to form giant cells. Mallory advocated the endothelial origin of the lung phagocyte strongly, and denied the phagocytic action of the alveolar epithelial cell.

In 1912, while associated with Klotz,^{102, 198} I made a series of studies on the development of pulmonary anthracosis, in part experimental, and

in part based on the anthracotic lungs encountered at autopsy in the Pittsburgh district. In the experimental work, I used india ink and finely ground lamp black, which was blown into the animals' larger air passages. I followed tubercle formation and giant cell development from wandering phagocytic cells, which were identified by their having taken up both the granules of pigment and the tubercle bacilli. The results obtained experimentally were supported by the studies on lungs removed at autopsy from human patients. In the study of the latter, a special stain was used which was not differential for the epithelium of the lung, but which made it possible to study the epithelium *in situ*. I found many alveoli filled with alveolar phagocytes in which the epithelial lining cells were intact and free from phagocytosed particles. I found alveoli in all the stages of pneumonia, with the air spaces full of so-called alveolar epithelial phagocytes, and with the lining cells still attached to the walls. Not once did I find pigment or other phagocytosed material in attached alveolar epithelium or in groups of definite lung epithelium which had desquamated in strips. I am convinced that the alveolar phagocyte is not of epithelial origin; but whether the cell is derived, according to Mallory's idea, from capillary endothelium; or, according to McJunkin,²³⁵ from the mononuclear cells of the blood; or, as stated by Gardner and Smith,¹¹⁷ from an interstitial lung cell—I am uncertain. I did not have sufficient evidence at the time to conclude, as I did, that it was a wandering endothelial cell of capillary origin.

A majority of present day authors are agreed that the giant cells of the lung come from the alveolar phagocytes, so that some review of the subject is necessary. For a detailed review of this phase of the question, the reader is referred to the comprehensive article by Foot.¹⁰⁷ The recent active interest in the origin of the alveolar phagocyte is closely associated with the advent of vital staining. Sewell,²³⁰ in 1918, studied vitally stained lungs, and concluded that the phagocytes were epithelial. His articles were answered by Foot,^{102,103} and by Permar,²⁵³⁻²⁸⁵ using various methods of vital staining; both authors supported the endothelial origin. Mallory and Medlar,²⁴³ reporting on the pathology of measles, demonstrated the presence of lung phagocytes associated with marked capillary endothelial proliferation in the lung. Their work was supported by Blake and Trask³⁸ in a study of experimental measles. Sewell, Aschoff,¹³ Kiyono^{185, 186} and Gross¹²⁷ actively maintained the epithelial nature; while Permar, Klotz^{192, 193} and, until recently, Foot¹⁰⁷ stood out for the endothelial nature of the phagocytes. Foot still denies their origin from epithelium, but admits the possibility of their derivation from blood monocytes and interstitial cells. Gardner, who formerly believed in the endothelial origin of the phagocytes, studied paraffin sections of lungs vitally stained with neutral red and concluded that the

phagocytes came neither from endothelial nor from epithelial cells, but from interstitial septal cells of the alveolar walls, and that they belonged, therefore, to the group of connective tissue phagocytes. Fried¹¹² begged the question by calling the alveolar epithelium a special kind of mesothelium which is able to desquamate and act in a phagocytic capacity. It may be noted, by way of comment, that any cell, whatever its nature, in passing from a capillary to the alveolus, must occupy the position of a septal cell during a part of the migration, and that the stain used by Gardner also stains the mononuclear leukocytes of the blood. While there is little evidence, under normal conditions, that the capillary endothelium of the lung is a source of mononuclear leukocytes, under inflamed conditions, the appearance is different; and the observations of Mallory in typhoid, and of Mallory, Medlar, Blake and Trask in measles, are hard to explain in any other way, save that the capillaries of the lung may, at times, become an accessory source of phagocytes.

The formation of giant cells from alveolar phagocytes is generally conceded by modern observers.

Origin of Giant Cells from Serosal Mesothelium.—The participation of the mesothelial or serosal epithelium in the formation of the tubercle giant cells and in the formation of foreign body giant cells has been noted by many workers. Marchand,²⁸⁰ from his earlier experiments with bits of sponge placed in the peritoneal cavity, described the proliferation of the mesothelial cells and their subsequent extension into the meshes of the sponge with the formation of giant cells. Herzog¹⁸¹ recently repeated Marchand's work, and reiterated his statement. Metschnikoff²⁶⁸ held a similar opinion. Karsner and Swanbeck¹⁸¹ reported the formation of giant cells in the pleura. Köster²⁰¹ studied the histogenesis of tuberculosis of the knee joint, and said that the giant cells developed from the serosal lining cells and from the endothelium of the lymph channels. Rindfleisch³⁰³ discussed the origin of giant cells from serosal endothelium in experimental tuberculosis of the omentum, by which he apparently meant mesothelium. Mesothelium is closely related to vascular endothelium in activity and appearance, but that it gives rise to wandering phagocytes is not universally conceded.

Origin of Giant Cells from Fixed Endothelium.—Beginning with von Schüppel,³²⁶ a great many observers have attributed the origin of giant cells to endothelial structures. Their theories fall into two classes: those which explain the presence of giant cells directly through changes in fixed endothelium, and those which have to do with endothelium as the source of wandering cells which later become transformed into giant cells.

For convenience of discussion, the theory of their origin from blood vascular endothelium and that of their origin from the lymph vascular

endothelium will be taken up, in turn, in the succeeding paragraphs, while the theory of their origin from wandering cells will be reviewed in the section on "exudative cells."

Ziegler credited Schüppel with being the first to advance the theory of the blood vascular origin of giant cells. According to Schüppel, the vessels in a tuberculous area become filled with a nonnucleated protoplasmic mass, the endothelium of the walls then proliferates and the appearance of a giant cell with peripheral nuclei develops; sometimes the vascular endothelium proliferates concentrically to such an extent that a complete cellular occlusion of the vessel occurs, and a giant cell with centrally placed nuclei is found. In a later article, in which von Schüppel³²⁸ identified "pearlsucht" in cattle with tuberculosis, he enlarged somewhat on his earlier views. He argued that a tubercle often starts within the lumen of a capillary where there are no lymphatics, and that since every tubercle has a giant cell as its beginning, this cell must be of blood vessel origin. Later, the vessel becomes closed and appears as a giant cell; the other surrounding tissues caseate, and only the giant cell remains to mark the site of the vessel. He felt certain that giant cells came only from blood vessels, and that the appearance was due to hyaline thrombi invaded by Cornil, Besançon and Griffon⁷⁶ reached similar conclusions from their studies of meningeal tuberculosis. Köckel¹⁹⁵ followed the formation of giant cells in the portal veins and concluded that they were thrombosed vessels, and that the appearance was due to hyaline thrombi invaded by endothelium which extended in from the vessel walls. Brodowski,⁵² Babes¹⁹ and recently Würm³⁸⁵ concluded that the giant cells of tuberculosis are anomalous outgrowths of endothelium from vessel walls. Brosch⁵¹ thought that giant cells could arise from capillary extensions which he called angioplasts, or from connective tissue cells which could take on endothelial characteristics and change to giant cells. He said that by proliferation of the endothelium of degenerated vessels, and in no other way, could giant cells with double rows of peripheral nuclei be explained. Rindfleisch (quoted by Langhans²¹¹), Deichler,⁸¹ Colberg⁷⁰ and Manz²⁴⁸ all supported the theory of the origin of giant cells from blood vessels, in some instances. Friederich and Noesske¹¹⁵ observed the formation of giant cells in the vessels of the kidney following the intravenous injection of tubercle bacilli. Miller²⁶⁹ and Bowman, Evans and Winternitz⁵⁴ studied the formation of tubercles from Kupffer's cells in the liver sinusoids. Foot¹⁰⁵ traced them in the meningeal vessels; and Gardner,²⁴ Medlar²⁶⁰ and Haythorn¹⁴³ found them in the vessels of the lungs and the spleen in experimentally produced tuberculosis. In such situations, the sources of giant cells are practically limited to endothelium and blood mononuclears.

The theory of the origin of giant cells from the endothelium of the lymph channels was held by Virchow, at first. Later, he accepted several other possibilities. Köster²⁰¹ and Hering¹⁵³ interpreted giant cells as cross sections of lymph channels with proliferated endothelial walls; and Cacciola⁶⁵ held a similar opinion, with the added conception of a thrombotic occlusion of the channel to explain the marginal situation of the nuclei. Tizzoni and Gaule³⁴⁵ accepted the view of Hering, but their descriptions and plates clearly show that the structures which they described as lymph channels were the retraction spaces of the ordinary miliary tubercle as we understand it today. They interpreted the clear space and the bits of caseous material so often seen in the center of a miliary tubercle as the lumen of the lymph channel. The partially or completely formed giant cells they took to be endothelial proliferations of the channel wall extending into the lumen. The roset of epithelioid, endothelioid or endothelial cells, they thought, represented the proliferated channel wall itself. Their observations on similar appearances in the testis have already been mentioned.

Klebs¹⁸⁸ was one of the earlier experimenters to follow the formation of tubercles and giant cells in lymph nodes. He found that the early tubercles began in the sinuses and developed from the cells of the endothelial lining. These at first became epithelioid cells and later formed giant cells. Manasse^{245, 246} reported similar observations. Ribbert³⁰⁰ and Lubimow²³⁰ favored the theory of the formation of tubercles and giant cells from the endothelial cells of the centers of the germ follicles of the lymph nodes.

Jacobson¹⁶⁸ reviewed all the possibilities of the formation of giant cells from vessels lined by endothelium; and concluded that giant cells might be cross sections of lymph vessels, but that it is unlikely, since they are constantly found in granulation tissues in which preformed lymph spaces do not exist; and that they are not thrombosed blood vessels, because thrombi in even the latest stages of degeneration contain occasional blood cells or fibrin which serve to identify them.

The various theories which assigned the origin of giant cells to cross sections of vessels were quickly overthrown with the general adoption of serial sections, by which it was found that the giant cells can be followed through comparatively few sections, while vascular structures often extend throughout an entire paraffin block.

Origin of Giant Cells from Exudative Cells.—In 1875, Ziegler³⁸⁸ issued a monograph on the formation of giant cells from exudative white cells. He implanted small glass plates cemented together in pairs in animal tissues. At first he placed the plates in the abdominal cavities of guinea-pigs, later in the pleural and pericardial cavities and finally in the intermuscular and subcutaneous tissues. In the latter locations, he

obtained satisfactory preparations and conducted seventy odd experiments. He removed the plates from day to day, and was able to follow the changes in the cells between them. He did not actually produce tubercles in this way, but did obtain all the cells ordinarily encountered in miliary tubercles, including typical giant cells. He concluded that tubercles could be formed from exudative cells alone, and that giant cells were formed especially from mononuclear cells, probably from both lymphocytes and large mononuclears. He did not assert that all tubercles and all giant cells were necessarily formed in this way, but he did think that it was possible. Ziegler's views met with active opposition on all sides, particularly from the authors who believed only in fixed tissue as the origin of the giant cells.

Marchand,²⁵⁰ in 1888, made extensive experimental studies of foreign body giant cells by placing pieces of sponge, hardened tissues of the lung, liver, blotting paper and other substances in the peritoneal cavities of guinea-pigs. He found the spaces of the sponges and the air spaces of the hardened tissue of the lung filled with exudative cells and granulations. Many of the preparations contained large foreign body giant cells. Marchand concluded that there were different kinds of giant cells, and that they were probably not all formed in the same way. He thought the large multinucleated cells were formed by fusion. He found many mitoses in the granulating areas adjoining, but none in the giant cells themselves.

Borrel,^{43, 44} in 1893, injected cultures of tubercle bacilli into the circulation, and stated definitely that giant cells were fused masses of mononuclear leukocytes. Yersin³⁸⁶ supported Borrel's view, which is now widely accepted.

The discussion as to the origin of the mononuclear leukocyte itself is still far from settled. Several relatively complete reviews on the nature of the large mononuclear leukocyte were published recently; the reader is referred to them for detailed information: Foot,¹⁰⁶ Sabin,³¹² Maximow,²⁵⁹ Jaffé¹⁷² and Sacks.³¹⁴ A brief summary of the views on the origin of the mononuclear leukocytes from which giant cells may be formed follows.

Some have held that mononuclear leukocytes are derived from vascular endothelium. Mallory,²³⁰ in 1898, discussing the pathologic changes of typhoid fever, pointed out the rapid proliferation of the capillary endothelium in that disease. He interpreted this proliferation as leading not only to the closure of some of the capillaries, indirectly causing focal areas of necrosis, and to ulceration of the tissues supplied, but also to the formation by the capillary walls of endothelial cells which become wandering mononuclear phagocytes. Subsequently, Mallory^{242a} interpreted this form of capillary proliferation as the source of all the mono-

nuclear leukocytes of the blood and tissues, including such variations as heart failure cells, compound granular cells, the cell essential in forming the miliary tubercle and foreign body giant cells. These cells, which he called endothelial leukocytes, he believed, fused to form giant cells. Mallory had many followers: McJunkin,²⁸⁵ Foot, Permar,²⁸⁶ Medlar,²⁸¹ Haythorn²³⁹ and others. Capillary activities similar to those in typhoid fever were reported observed in measles by Mallory and Medlar²⁴³ and by Blake and Trask;⁸⁸ in typhus by Wolbach, Todd and Palfrey;³⁸³ in Rocky Mountain fever by Wolbach,³⁸² and in tularemia by Permar and Wiel.²⁸⁷ Foot¹⁰¹ and McJunkin subsequently modified their views somewhat, questioning the origin of nongranular monocytes exclusively from vascular endothelium. Sabin, Doan, Cunningham and others considered that some of the mononuclear leukocytes are formed by proliferation of capillary endothelium, and that others belong to the myelogenic group. F. A. Evans⁹⁸ accepted their interpretation.

Others have held that the mononuclear leukocytes take their origin from "reticulo-endothelium." Some of the early pathologists used the expression "endothelium of the reticulum of the germ centers" in discussing tuberculosis. The work of Downey,⁸³ Aschoff¹³ and Kiyono¹⁸⁵ established the term in its present sense. Reticulo-endothelial cells are defined as endothelium resting on a special reticulum, which are phagocytic in situ and take up vital stains readily. The reticulo-endothelial system includes the endothelial cells lining the sinusoids of the liver (Kupffer's cells) and similar cells of the spleen, bone marrow and lymph nodes. Aschoff, Kiyono and others, working with vital stains, attributed the origin of part of the mononuclear leukocytes of the blood and tissues to reticulo-endothelium. Mallory and Parker²⁴⁴ showed recently by a long series of microchemical reactions that the reticulum supposed to be formed by endothelium is really collagen, and is derived from connective tissue cells. They stated that endothelial cells do not form reticulum. Since all the endothelium of the body rests on connective tissue, and a group of cells capable of forming a special reticular substance does not exist, the use of the term reticulo-endothelium to denote a specific group of endothelial cells does not seem to be sufficiently differential to be justified.

Other authors have supported a lymphocytic origin of mononuclear leukocytes. After the early work of Ziegler, numerous authors concluded that lymphocytes change into large mononuclear wandering cells and later into epithelioid and giant cells. Recently, Maximow²⁸⁸ and Bloom⁴² published the results of studies of tissue cultures; they concluded that lymphocytes change into large mononuclear wandering cells, which Maximow called "polyblasts." In his work on the development of tubercles in vitro, Maximow reported that "polyblasts" arise

partly from local "resting wandering cells" of the tissues (such as clasmatoocytes and histiocytes) through rounding off and mobilization; and partly from lymphocytes, nongranulated white blood corpuscles and monocytes which may migrate from the vessels or which may have been previously present in the tissues. The polyblasts hypertrophy and join the local histiocytes, become ameboid phagocytic cells and change into epithelioid cells, which may later fuse to form giant cells. According to him, the vascular endothelium does not take part in the process. He concluded with the statement that lymphocytes are slower, but, nevertheless, become transformed into epithelioid cells.

Here the views of Mallory and Maximow are directly opposed on two important points, Mallory holding that the large mononuclear cells which become epithelioid cells come from endothelium, and that lymphocytes never become phagocytes; Maximow, that vascular endothelium does not play a part in the formation of mononuclear cells, and that lymphocytes change into phagocytes and epithelioid cells.

Perhaps the stains used have something to do with the disagreement. Maximow used hematoxylin and azure II. Mallory fixed his material in Zenker's solution and stained with eosin-methylene blue or phloxin-methylene blue. The latter stain is highly differential for the cells of the lymphocytic series and for mononuclear cells in tissues; and while lymphocytes and plasma cells stain alike, I have not yet seen any cell that still retained the violet tinge of the lymphocyte-plasma cell series acting as a phagocyte.

Wandering Phagocytes of the Tissues.—Perhaps no other cell in the body has given rise to so much discussion as the wandering large mononuclear phagocyte of the tissues. Views differ on its nature and origin, and as to whether it is a local product having a specific function, or merely appears temporarily from the general circulation in response to a stimulus. It seems best to review briefly the conclusions concerning this cell, even at the risk of repeating part of the data covered by the paragraph on exudative cells; for this cell, whatever it actually is, plays an important rôle in the formation of giant cells. According to Mallory,^{242a} it is of vascular endothelial origin, and is identical with the endothelial leukocyte of the general circulation. According to Sabin,³¹² it may be either of two cells, one of which comes from endothelium and the other from the myelocytic series. Aschoff¹⁸ classified it as a tissue histiocyte of reticulo-endothelial origin. Maximow²⁵⁷ called it the "resting wandering cell," or "polyblast," and derived it primarily from the mesoderm, but also from wandering lymphocytes. Ranvier²⁹⁶ called it the clasmatoocyte. Simpson³³¹ called it a macrophage, and, by the use of vital stains, separated the macrophages from lymphocytes. McJunkin,²³⁵ by the use of the benzidene reaction and by staining with

neutral red, identified three types which he called monocytes, lymphendotheliocytes and hemendotheliocytes, the lymphendotheliocyte being the one which he considered the source of the epithelioid cells, but which is not related to the lymphocytes. These cells appear to be the same as those called pyrrhol cells by Goldmann;¹²³ macrophages by Metschnikoff²⁰⁰ and Evans;⁹⁴ monocytes by Pappenheim;²⁸¹ adventitial cells by Marchand,²⁵⁵ and so on. Karsner,¹⁷⁸ after carefully reviewing the question in his recent textbook, attempted to be impartial, adopting two new terms: namely, "endotheliocytes" and "endothelial phagocytes."

Whatever the exact nature of this cell may be, and whether it represents a single specific cell or a group of closely allied cells, it is this cell or cell group which is most intimately concerned in the formation of the Langhans or foreign body giant cells.

THEORIES OF THE FORMATION OF GIANT CELLS

In discussing the theories of the formation of giant cells, the cell in question is the foreign body giant cell, including the Langhans cell of tuberculosis and the osteoclast. Langhans, in his original article, said that there were two ways in which these cells might be accounted for: (1) by division of the nuclei without division of the cell; and (2) by the fusion of several cells to form a single large cell. Each theory has had numerous adherents, and the question of the correctness of either to the entire exclusion of the other has not yet been settled. It is known that nuclei may divide without the complete division of the cell, in many instances, and it is conceded that this is the usual process of formation of the multinucleated muscle repair cells, megakaryocytes, epithelial syncytia and tumor cells. It has been proved, also, that cells of the types from which giant cells are formed may fuse to form large single cells in cultures. It is likely that either or both of these processes may take place in the living animal, depending on external influences and environmental conditions. The time required for the formation of giant cells has usually been given as varying from about eight to fourteen days in experimental animals, and even less in tissue cultures. Marchand obtained his most beautiful pictures in about thirty-five days.

Nuclear Proliferation.—A great many observers have accepted the theory of nuclear division to account for multinucleated giant cells, in spite of the fact that mitotic figures in these cells are of extremely rare occurrence. Krompecher²⁰³ made an extensive investigation of cellular division, and applied his researches in part to osteoclasts. He said that the nuclei could divide by mitosis or by amitosis including direct division, and by direct and indirect fragmentation. Mitosis might be single, double or multiple, leading to two, four or many nuclei, respectively, and followed a proliferative stimulus in a healthy growing cell. Amitosis could

take place by direct division, which was the simple constriction of the nucleus and its division into two equal parts; or by direct fragmentation, in which bits of the nucleus were snared off in a manner resembling budding; or, finally, by indirect fragmentation, in which the particles of chromatin became diffused throughout the cell and rearranged into two or more nuclei. Amitosis took place in poorly nourished or degenerated cells, though it was possible for both mitosis and amitosis to go on simultaneously in the same cell. Mitosis meant a progressive lesion; amitosis indicated a retrogressive one. He emphasized the theory in embracing Weigert's conception of the formation of giant cells in tuberculosis. Weigert believed that when tubercle bacilli became localized in an area, they were taken up by cells which then underwent rapid proliferation by mitotic division. The tubercle bacilli also multiplied and produced a toxic effect on the cells, so that when mitosis began in the usual way, the vitality of the cell was so lowered that division was limited to the nuclei, and complete division of the cell could not follow. Later, the central portion of the cell died, and the nuclei continued to live and multiply in a zone of living protoplasm in the periphery. Baumgarten,^{80, 80a} who was an early advocate of nuclear division, taught that giant cells were formed by multipolar division of fixed cells. He did not believe that fusion could occur as a part of an active process which led to multiplication of all the cells in the area. Later, he accepted Weigert's explanation, and since both were emphatic in their stands that the giant cell was the result of a combination of multiplication and degeneration of fixed tissues the theory has become widely known as the Baumgarten-Weigert theory.

The advocates of mitotic division of nuclei have been comparatively few. Cornil,⁷⁴ Manasse,²⁴⁶ Goldmann¹²² and Foot¹⁰⁴ described mitotic figures. Hammerl¹⁸⁵ saw one figure; Justi observed two instances of mitosis, but was a strong believer in direct division. Mallory, in a personal statement to me, said that he had not found a mitotic figure in a giant cell which could not be explained on the basis of a cell that had been phagocytosed during mitosis. I have been shown two instances of mitosis in giant cells: one by Gardner and the other by Cohen. I think that Mallory's explanation could be applied in both instances, but it is difficult to establish this point. Advocates of direct division have included Koch,¹⁰⁴ Duval and White,⁶⁸ Lubimow,²³⁰ Pilliet,²⁹² Köster,²⁰¹ Lubarsch,²²⁸ Bakacs,²³ Vierordt,²⁴⁸ Straus and Gamaleia,³³⁹ Goldzieher and others. Arnold⁸ was the chief advocate of fragmentation of the nuclei. In an effort to settle the question of nuclear division in giant cells, Wakabayashi,³⁵⁰ working under Benda's direction, studied certain inclusions in giant cells with Heidenhain's iron hematoxylin and a method devised by Benda. He demonstrated certain bizarre spheroids

in giant cells fixed in Flemming's solution, which he interpreted as pathologic centrosomes and centrospheres. His observations were confirmed by Herxheimer¹⁵⁸ and by Herxheimer and Roth,¹⁵⁹ and questioned by Joest¹⁷⁴ and others, who suggested that they were probably Wolbach's inclusions.

The Formation of Giant Cells by Fusion of Cells.—The fusion theory has been the most widely adopted of all the theories of the formation of giant cells. The earlier arguments in its favor were based chiefly on the absence of mitotic figures. Some authors applied the observation of fusion of phagocytes in starfishes, reported by Metschnikoff and Adami,¹ and a similar observation made on frogs by Lange²⁰⁹ to pathology in human beings. Arnold, who favored fusion, as well as nuclear fragmentation, believed that the mosaic arrangement of the nuclei suggested fusion. Langhans, as has already been stated, favored fusion because of the platelike arrangement and similarity of the nuclei of the adherent "cell mantels." Krause²⁰² thought that if nuclei multiplied by division, they should occur in even numbers, which they were not likely to do by actual count.

More recently, Mallory²⁴² explained fusion on the basis of overstretched surfaces of phagocytic cells and changes in surface tension. Wells²⁷⁷ also explained the formation of giant cells as a combination of chemotactic phenomena and changes in surface tension. He stated that the cells, especially those of the reticulo-endothelial system, move toward an attracting particle, and when that particle is large, the cells spread out on its surface, and their contents of cytoplasm flow together because of their altered surface tension. The peripheral position of the nuclei depends on the fact that, in ameboid motion, the nucleus is entirely passive, is dragged along by the cytoplasm and, hence, is farthest from the attracting particle. Ziegler,³⁸⁸ Borrel,^{43, 44} Leray,²¹⁷ Lange,²⁰⁹ Wechsburg,²⁶⁷ Mallory,²⁴² Forbes,¹⁰⁸ Burgess,⁵⁰ Wells²⁷⁷ and others favored fusion of white cells generally. Weiss,³⁷⁸ Walb³⁵⁷ and Ewetzki⁹⁵ worked on exudates in the cornea, and concluded that giant cells were formed by the fusion of white corneal corpuscles; and Senftleben,³²⁰ using similar methods, included lymphocytes in the fusion as well. Schüppel,²²⁶⁻²²⁸ Birch-Hirschfeld,⁸⁷ Ribbert,³⁰⁰ Bredichin,⁴⁸ Klebs,¹⁸⁸ Mai,²⁸⁰ Franchetti,¹¹⁰ Kiener¹⁸⁵ and others believed in the fusion of fixed endothelial cells; and Schmauss and Urshinsky in the fusion of epithelioid cells. Warren³⁵⁰ applied Bielschowsky's silver method, and demonstrated a reticulum in giant cells similar to that between the pre-existing surrounding cells; this, he thought, indicated fusion. Lambert,²⁰⁵ Cohen,⁶⁰ Lewis^{220, 221} and Maximow²⁵⁸ observed fusion actually taking place in tissue cultures.

Haythorn¹⁴⁰ and Permar²⁸⁶ favored fusion on the ground of the distribution of the phagocytosed granules of carbon. Karsner and Meyers¹⁸⁰ reported the fusion of alveolar epithelial cells to form giant cells in organizing pneumonia, and Waldstein³⁵⁸ described a fusion of epithelial cells in the germinal tubules. Numerous others, who accepted other views, included fusion as an alternate possibility.

Formation by Combined Nuclear Multiplication and Fusion.—Several authors favored the theory that giant cells were formed by combined nuclear division and fusion of cells, while others believed that one process could take place at one time and the other at another.

Metschnikoff²⁶⁶ described fusion in *Bipinnaria* and in *Astropecten*, and applied the theory generally until he studied tuberculosis in a small gopher-like animal, the Ziesell; here he found nuclear multiplication evidenced by mitoses. Stschnastny,³⁴¹ one of his pupils, repeated his experiments on the Ziesell, also found evidences of nuclear multiplication, saw a mitotic figure and so concluded that the formation of giant cells was different in varying species. Adami¹ made a distinction between those mesothelial cells about foreign bodies in the body cavity of the astropecten which multiplied to form a "plasmodium," and those which fused to form a "syncytium." Manasse,²⁴⁶ Marchand²⁵⁰ and Herzog¹⁶¹ found that epithelioid cells in early tuberculosis often contained mitotic figures, and that these cells were easily differentiated up to the two-four-eight nuclear stage. They evolved the theory that multiplication took place until the cells became large enough to produce an attractive force, after which they fused with similar cells to form giant cells. Kostenitsch and Wolkow²⁰⁰ thought phagocytes wandered into free foci of plasma exudate, proliferated, at first, and later fused to form giant cells. Joest (cited by Stschnastny³⁴¹) favored fusion, but thought either could happen. He said that the lymphocytes did not fuse to form giant cells, and that when they were present within giant cells, it was due to their having been phagocytosed. Bakacs described two stages in the formation of giant cells, one of primary degeneration, and a later stage of nuclear proliferation. He thought that the presence of giant cells indicated a progressing lesion, and their absence a healing one.

Additional Theories of the Formation of Giant Cells.—Köckel¹⁹⁵ discussed the relative merits of fusion and nuclear division at some length, and while he favored fusion, he suggested a rather novel way of accounting for it. He pointed out that dead cells were known to be phagocytosed by living cells, and also that Krückmann²⁰⁴ had shown that living cells might penetrate dead cells, so that one possible way in which fusion could come about was for the more active one of two giant cells to phagocytose the other. Similar views have been expressed since.

Guieysse-Pellissier¹²⁰ suggested that when single cells died, their chromatin was broken up and extruded, and was then reabsorbed by giant cells and formed into new nuclei.

Several authors suggested that giant cells were not true cells, but in reality only artifacts resembling cells. E. Wegner³⁰⁸ and Arnold⁹ thought some giant cells were formed by sudden areas of degeneration in the centers of groups of cells. Kostenitsch and Wolkow suggested that giant cells might be nothing more than areas of coagulated plasma, either in the connective tissues or in vessels, and that the appearance of being a giant cell was due to separate cells which wandered into the periphery of the plasma zone and underwent proliferation. If this were the case, the size, shape and appearance of the so-called giant cell would depend on the pressure and comparative rigidity of the surrounding tissues. Medlar²⁶¹ recently published an opinion somewhat similar. He considered that the giant cells of tuberculosis did not appear until after necrosis had set in. He studied their formation with human, avian and bovine strains; and concluded that, in each instance, areas of necrosis developed and were invaded by mononuclear leukocytes, lymphocytes and polymorphonuclear leukocytes. The infiltrating cells might pass to the centers of the dead inflammatory tissue or remain in the borders, giving the typical appearance of peripheral or central arrangement of nuclei, respectively. He stated definitely that giant cells in tuberculosis were not cells, but only infiltrated caseous foci.

When Medlar reported his views, I was studying the effects of edema on tuberculous lesions in rabbit ears and at once I turned my attention to his observations. I found that where edema or a serous exudate was produced in early tubercles formed in tissues marked with india ink, the giant cells separated in one of two ways: some separated out as sharp cellular structures with definite outlines, showing them to be true cells; while others broke up and separated out as fragments of necrotic tissue with single and smaller multinucleated cells. I think Medlar's idea explains a stage of the formation of giant cells, but is limited to a step in development. The majority of tuberculous giant cells are true cells.

The various theories which accounted for giant cells on the basis of their resemblance to cross sections of vessels and associated characteristics have already been discussed.

METHODS USED IN STUDIES OF GIANT CELLS

The methods used in studies of giant cells have embraced almost all the procedures known to pathologists. Beginning with the examination of unstained smears and teased preparations, and progressing through the simple staining of sections of tissues embedded in celloidin, the special staining of sections from tissues prepared in paraffin, the experimental production of lesions known to produce giant cells, the vital

staining of tissues and the cultivation of tissues in vitro—each new method has added something to the knowledge not only of the giant cell, which in itself is comparatively unimportant, but to the knowledge of the nature of the related diseases and of the bodily means of resistance and defense.

It is my purpose to review briefly the methods used, and cite, when possible, the main fact or facts which each method has uncovered.

Fresh Preparations.—Giant cells were first described in smears, teased preparations and scrapings mounted in physiologic sodium chloride solution, in glycerin or in weak acetic acid. Langhans²¹¹ reported his results with fresh tissues, and demonstrated that giant cells are not necrotic foci with cellular infiltration, but true multinucleated cells. Metschnikoff²⁶⁸ and his followers studied phagocytosis by macrophages in fresh preparations and smears, and contributed the fundamentals of giant cell function. Koch¹⁹⁴ described the presence of bacillary masses in stained smears; and almost all authors who have worked with intraperitoneal inoculations of tubercle bacilli have made cytologic studies of the exudate as a part of the work. These methods are all useful, and receive altogether too little attention at present.

Sections of Fixed Tissues.—By far the greater number of studies reported have been of fixed tissues. These studies have added much of the accurate knowledge which is at hand, and some of the confusion which exists. Limited at best, the study of fixed tissues has been further hampered, in innumerable instances, by the use of more or less inefficient fixatives and imperfect staining methods and by the inadequate training of some of the observers. Much of the early work was done by simple nuclear staining with carmine. Later, hematoxylin became the vogue, and has held its place to this day in many laboratories. Eosin, erythroxin, phloxin and azure II have been the more commonly used counterstains, though none of them is differential for blood or tissue cells. Mallory²⁴⁰ introduced the use of eosin-methylene blue on tissues fixed in Zenker's solution, and more recently advised a change to phloxin-methylene blue. In my experience, this method has been the most valuable for the study of giant cells and other forms of exudative cells. Because of its polychromatic staining of the cytoplasm of the lymphocyte-plasma cell series, one is able to distinguish clearly this series of cells from the large, nongranular mononuclear leukocytes, and to detect the differences between the nuclei which characterize the multinucleated giant cells and those of lymphocytes or plasma cells which may have been phagocytosed. Giemsa's stain has been used for similar purposes, but is not easily applied successfully to tissues.

The special stains which have been applied to the nucleus have been used to bring out the nuclear changes which have to do with nuclear

division, and have been made for the purpose of settling the question of fusion or division. Heidenhain's hematoxylin (Schmorl^{323a}), Benda's hematoxylin (Schmorl^{323b}) and Benda's special stain to bring out structures connected with nuclear changes, centrosomes and centrospheres (Schmorl^{323c}) were used by Wakabayashi,³⁵⁶ Herxheimer,¹⁵⁸ Herxheimer and Roth¹⁵⁹ and Herzog¹⁶¹ with more or less divergent conclusions, as already has been noted.

Chemical reactions for iron, fat crystals, soaps, glycogen, collagen, colloid and elastic tissue were used by Herxheimer, Wolbach, Iwanoff and others in an attempt to identify certain inclusions which they encountered.

Modifications of the Gram-Weigert and of all the acid-fast bacterial stains have been used in the study of the included organisms and the yellow central bodies described as masses of dead tubercle bacilli by Weigert and Koch. Through the use of connective tissue and fibril stains, such as Mallory's stain for connective tissue, phosphotungstic acid hematoxylin, Bielschowsky's silver method and Van Gieson's stain, it has been possible to show that giant cells may include collagen fibrils. Weigert's stain for elastic tissue has shown that fibers of elastic tissue may become potent foreign bodies leading to the development of giant cells. The stains for reticulum were used to advantage by Downey,⁶³ Warren,³⁵⁹ Foot,¹⁰³ and others in their studies of reticulo-endothelium. Mallory and Parker²⁴⁴ employed similar methods to show that endothelial cells do not form reticulum.

Many attempts were made to differentiate tuberculous giant cells from osteoclasts, and while it was sometimes possible to show acid-fast organisms in one, and alkaline granules in the other, a consistently reliable method has not been found, and this is an additional point for their cytologic identity.

Vitally Stained Tissues.—Vital staining has added a great deal to our knowledge of tuberculosis, the formation of foreign body cells and exudative lesions generally. The first account of vital staining which I found was that of Walb,³⁵⁷ who injected the cornea of rabbits with carmine solution and found that the corneal corpuscles became stained, while the leukocytes did not take up much carmine. He traced the formation of foreign body giant cells from the stained corpuscles. Senftleben³²⁹ and Emil Marchand²⁴⁹ performed similar experiments, but did not confirm Walb's conclusions. F. Marchand²⁵⁰ injected gelatin stained with methylene dyes, and produced foreign body giant cells containing stained phagocytosed particles. Oppenheimer,²⁷⁴ Goldmann¹²³ and Bowman, Evans and Winternitz⁵⁴ studied the formation of tubercles from vitally stained Kupffer's cells in the liver. Haythorn,¹³⁹ and later Foot¹⁰¹⁻¹⁰⁵ and Permar,²⁸⁵ injected india ink in studying the formation of tubercles and giant cells. McJunkin²³⁴ marked

mononuclear leukocytes with finely ground lamp black. Sewell,³²⁰ Permar,²⁸⁴ Simpson,³³¹ Foot, Sabin, M. R. Lewis and W. H. Lewis,²¹⁹⁻²²² and others used pyrrhol blue, neutral red, trypan blue, trypan red, colloidal carmine, Niagara blue, isamine blue and the benzi-dine reaction in identifying the large mononuclear leukocytes. Gardner¹¹⁶ and Cash⁶⁶ separately devised ways of studying cells vitally stained with neutral red in paraffin sections.

By means of these methods of vital staining, it has been possible to relegate the activities of fixed tissues to the background in the formation of giant cells and to emphasize the importance of the large mononuclear phagocytic cells.

Experimental Studies.—The most interesting work which has been done on giant cells is that along experimental lines. One of the earliest groups of experiments in which giant cells were found was performed by Conheim and Frankel⁷² in 1869. Apparently they were interested in giant cells only as one of the diagnostic points of tuberculosis. They transplanted bits of caseous material into the peritoneal cavities of guinea-pigs, and obtained tubercles. They then took bits of normal tissue from tuberculous cadavers, and again obtained tubercles. The work preceded the days of sterilization of instruments, and after they had injected all sorts of things, including blotting paper, clean lint, gutta percha, india rubber and the like, they obtained tubercles with giant cells in all the animals which survived acute general peritonitis. They decided from their experiments that tuberculosis was not due to a specific virus, but came from a variety of substances. Lange²⁰⁹ studied the reactions in the lymph sac in frogs, and found giant cells. Weiss,³⁷³ after finding giant cells about coal dust and in a syphilitic bubo, injected hairs, woolen fibers and feathers into the subcutaneous tissues of animals and studied the process of encapsulation. He found rather large cells with single nuclei about the foreign substance. They suggested epithelial cells, but were not, and some of them had from two to four nuclei. There were also well developed giant cells which he thought came by fusion of the smaller ones.

Ziegler's³⁸⁸ experiments with glass platelets have already been discussed. Emil Marchand,²⁴⁹ in 1883, working under the direction of Baumgarten,²⁵ implanted silk sutures and sponges in the tissues of guinea-pigs. He used two series, one with iodoform crystals, and one without. He noted that organization of the sponge took place by the extension of connective tissue and capillaries into the meshes, and decided that giant cells came from the ingrowth of fixed tissues. The giant cells appeared in the peripheral areas of the sponge, while the infiltrated areas were in the more central portions. He also repeated Walb's²⁵⁷ and Senfleben's experiments with modifications. Walb, in 1876, had injected the cornea of living rabbits with carmine solution, and

found that ordinary white cells and lymphocytes were not stained, but that true corneal corpuscles took up the carmine. He traced giant cells to the fusion of the stained corneal corpuscles. Senftleben, in exactly similar experiments, had concluded that they came from fused lymphocytes. E. Marchand injected the cornea of a dead rabbit, removed it and used it as a foreign body in another animal. In two days, all the pus cells about it were stained with carmine; he therefore thought the method inconclusive. E. Marchand verified the observations of Baumgarten as to the relationship of giant cells to blood vessels, and concluded that giant cells are always formed from fixed tissues.

Hallwachs¹³³ was one of the early workers to use antiseptics to exclude the inflammatory reactions in the healing of injuries caused by various foreign bodies. Other early experimenters included Heidenhain (quoted by Langenbeck²¹⁰), who injected elderpith; von Recklinghausen²⁰⁷ and Ranvier,²⁰⁵ who injected blotting paper and a substance called "Lammanariastücke," and von Lesser,²¹⁸ who reported on the reactions formed about catgut sutures.

Felix Marchand, in an important contribution in 1888, injected sponge, small pieces of the hardened lung of a human being in place of a very firm sponge, hardened liver, pieces of cork, blotting paper, rabbits' cornea and stained gelatin. Marchand²⁵⁰ found sponge of fine grain the best material for the study of giant cells, and credits Hamilton¹³⁴ (1881) with having been the first to use it. Marchand²⁵⁰ made many experiments, including the injection of stained gelatin and lycopodium spores; and concluded that giant cells came in part from the cells in the immediate surroundings, and possibly also from wandering cells. He credited Martin²⁵⁶ with first using lycopodium spores. Later, von Bunge, working under Marchand, used foreign bodies dipped in turpentine or iodoform, and verified Marchand's observations. Herzog,¹⁶¹ another of Marchand's pupils, repeated the experiments with sponge grafts in 1916, saying that he wished to study the results with modern technical methods and modern differential staining, and in the light of recent conclusions with reference to blood cells. He concluded that foreign body giant cells came from mononuclear leukocytes, serosal mesothelium and connective tissue cells in the submesothelial areas, and resulted from nuclear proliferation.

Faber⁹⁷ first injected agar-agar. Forbes,¹⁰⁸ working under the direction of Mallory and Wolbach, studied the origin of foreign body giant cells about injections of agar-agar. In 1922, I^{139,140} made some experiments by injecting stained agar-agar, agar-agar mixed with lycopodium spores and agar-agar mixed with lycopodium spores stained, before injection, with gentian violet. I injected india ink to mark the cells, and it seemed to me that giant cells in these foci were formed by the fusion of mononuclear phagocytes. Later I produced lesions in

similar ways, and followed them by inducing localized edemas or serous exudates about them. I was interested in separating the tubercles, and particularly the giant cells, into their constituent elements. Some giant cells broke up into a central caseous mass with a margin of phagocytes and other cells, as stated by Medlar,²⁰¹ but the majority of the giant cells separated out as definite cellular entities.

No other type of foreign body has been used in the production of giant cells so frequently as tubercle bacilli and their products. It is impossible to review the experiments here, though the results of many have been given. Particularly worthy of mention is the experiment of Kostenitsch and Wolkow,²⁰⁰ who produced chronic inflammatory exudate of mononuclear cells by injections of albumin before the injections of tubercle bacilli. Also worthy of mention is the work of Pruden and Hodenpyle,²⁰⁴ who were the first to show that giant cells are formed in lesions produced experimentally by the injection of dead tubercle bacilli. Of interest also, was the experiment of Burgess,⁹⁹ who injected the chemical constituents of caseation necrosis synthetically prepared by mixing calcium phosphate, calcium carbonate, cholesterin, palmitic and stearic acids and several bland oils and fatty substances extracted from tubercle bacilli, and obtained giant cells, thus showing conclusively that the giant cell of the tubercle is only a type of giant cell and not a specific structure.

Tissue Cultures.—Awrorow and Timofejewski¹⁷ paved the way for the study of cultures of blood cells in vitro. In the hope of settling the question between fusion and nuclear division, many workers turned to this field. The possibility of fusion to form giant cells has been definitely settled, so far as embryonic cells and the cells of some of the lower animals are concerned, but the observation of giant cells in cultures has not always led to uniform conclusions. Several research workers, who formerly believed that giant cells were formed exclusively by direct nuclear division, later reported the observation of fusion. Lambert and Hanes²⁰⁶ observed giant cells of great size, from 30 to 500 microns in diameter, in cultures of spleen and bone marrow of rats. They interpreted the cells as the result of unsuccessful cell division. In 1912, Lambert,²⁰⁵ in studies of cultures of the spleens of embryo chicks, reported the observation of a fusion of cells to form the large giant cells. In 1921, Lewis and Webster,²²³ working with cultures of human lymph nodes, described the formation of giant cells by amitosis from endothelial cells which corresponded to the reticular cells of Maximow. Lewis and Lewis²²² stated definitely that, in cultures of human lymph nodes, giant cells were not formed by fusion. Subsequently, Lewis and Bruda²²¹ observed a fusion of mononuclears to form large giant cells, and still more recently in 1927, Lewis,²²⁰ in cultures of rat sarcoma, reported the formation by fusion of giant cells in all respects typical of

the Langhans giant cell of tuberculosis. He published a series of sketches made at intervals of from fifteen to twenty minutes, which illustrated the fusion. In the same cultures, he observed direct nuclear division without division of the cell. Giant cells appeared in his cultures to be formed, in part, by direct division, mitoses not having been seen; in part, by fusion of separate cells; in part, by the incorporation of additional single cells with the giant cell, and in part, by the fusion of two or more multinucleated giant cells to form larger giant cells.

Cohen,⁶⁹ using Sabin's⁸¹³ technic with neutral red, studied cultures of turtle's blood and saw cells fuse to form giant cells. Later he found that giant cells may break up and form smaller multinucleated cells. Maximow²⁰⁷ studied the formation of giant cells in tissue cultures to which tubercle bacilli had been added, and found that tubercles were formed from "polyblasts," which he stated were the same cells as the "macrophages" of Metschnikoff. He stated that these cells originated, in part, from resting wandering cells of the connective tissues and, in part, from nongranular white cells and monocytes. He observed the transformation of polyblasts into epithelioid cells and giant cells. The latter were formed by the fusion of epithelioid cells. Lang,²⁰⁷ working with cultures of rabbit lung and tubercle bacilli, traced the formation of tubercles to the interalveolar septal cells, but did not observe any formation of giant cells.

Analyzing the evidence from tissue cultures, I find that the formation of giant cells by fusion cannot be excluded; and it seems probable that direct nuclear division, though much harder to prove than fusion, also occurs.

Reconstruction.—Medlar presented some interesting serial section reconstruction models of giant cells at the Meeting of the International Museums Society in Albany in 1926.*

FUNCTIONS OF GIANT CELLS

The earliest idea of the function of the giant cell was that held during the period dominated by the "blastema" theory of cell origin. Giant cells were then supposed to be centers for the spontaneous development of exudative cells. According to Langhans, Rokitsansky³⁰⁷ described giant cells in his treatise on pathology as "mutterzellen," or large multinucleated protoplasmic structures with many free mononuclear cells gathered about them. They were believed to act as small "pseudo-peritoneal" membranes and to produce tubercle cells spontaneously. This view was practically given up with the general adoption of Virchow's theory, "omnis cellula e cellula."

* The Bulletin of the International Museums Society, containing a report of the Albany meeting, has not yet appeared.

Metschnikoff²⁶⁵ maintained from the beginning that giant cells were multinuclear phagocytes, and that they originated from unicellular phagocytes. This view has now come to be almost universally adopted. Opposed for many years to this view were the theories of Baumgarten²⁸⁻³⁰ and Weigert,³⁷² which postulated that giant cells were primarily centers of destruction and were doomed from the moment of their appearance. It followed from this hypothesis that giant cells did not have a function, but were only stages in necrotic changes. Even Weigert, however, described yellow nodular inclusions in giant cells, which he believed to be dead bacilli. Other theories have attributed ameboid motion to giant cells, which permitted them to wander about and distribute tubercle bacilli. Schmaus and Urshinsky³¹⁹ considered them as centers for the beginning of a tubercle. The present interpretation connects them with the incorporation of necrotic matter, crystals and anything insoluble which is deleterious to the tissues and is absorbed either slowly or not at all. On account of this phagocytic activity, Smith³³² considered giant cells as evidence of the highest resistance of a tissue against tuberculosis.

There is no longer any question that the chief function of giant cells is one of defensive phagocytosis. Zinsser³⁹¹ credited Panum²⁸⁰ with having been the first to suggest that phagocytosis plays an important rôle in combating infectious diseases. Metschnikoff²⁶⁵ was the real founder of the school which taught that phagocytosis was the body's chief mechanism of defense. He divided phagocytes into fixed and ameboid phagocytes. The fixed type were lining cells, for example, Kupffer's cells; the ameboid type consisted of (1) microphages, or polymorphonuclear leukocytes, and (2) macrophages, or mononuclear phagocytes. Metschnikoff thought that giant cells were an active mechanism of defense against tuberculosis, that they developed from the macrophages and that they were themselves active ameboid phagocytes. Stschnastny, one of Metschnikoff's pupils, said that giant cells devoured tubercle bacilli by their very voracity and that, though the bacilli multiplied when first taken up, they were eventually destroyed. Di Renzi²⁹⁹ concluded from his researches on giant cells in tuberculosis that the bacilli were taken in and underwent multiplication for a time, but that later waxy capsules formed about them, and these became fused into yellow clumps of dead bacilli. Koch¹⁹⁴ also described the waxy yellow inclusions and interpreted them as dead organisms. He did not consider that the result was in any way due to the activity of the cell. Welcker studied phagocytosis of tubercle bacilli on the warm stage and found that the cells took up bovine bacilli quickly and underwent caseation, but that they phagocytosed human and avian strains much more slowly. With reference to streptococci, Gay and Morrison¹²¹ considered phagocytosis to be the chief agent of defense. Borrel^{42,44}

and Kiener¹⁸⁸ were also advocates of phagocytosis by giant cells as an important defensive reaction. Köckel¹⁹⁵ believed that giant cells phagocytosed not only tubercle bacilli and exudative cells but also each other. Lange²⁰⁰ observed phagocytosis of cells by multinucleated cells in puncture fluids from the lymph sac of frogs.

Karsner,¹⁷⁹ in his new textbook, outlined phagocytosis briefly in three phases: (a) the stage of approach, which he attributed to chemotaxis; (b) the stage of ingestion due to mobility of the phagocyte, stickiness of the cell wall and changes in the surface tension and in the hydrogen ion concentration, and (c) the stage of destruction or digestion of the particle. Formerly, there was some doubt as to the power of a cell to digest incorporated material. Faber,⁹⁷ in 1893, demonstrated the power of giant cells to digest agar-agar. The preparations of Ssudakawitsch, showing digestion of elastic fibers, were convincing; some of the elastic fibers were long enough to extend beyond the borders of the cell and such extracellular portions were preserved, while the intracellular parts were partially digested. Opie²⁷³ demonstrated the enzymatic action of phagocytes on tubercle bacilli. Maximow²⁵⁷ followed the formation of tubercles in cultures of mammalian tissues and observed the phagocytosis of tubercle bacilli and their subsequent digestion. He stated that the intracellular digestion of bacilli in epithelioid cells is probably highly increased after their fusion into giant cells, so that the number of organisms in the multinucleated cells is never great. Later, the giant cells contain inclusions of yellow pigment resulting from destroyed bacilli. Wells²⁷⁷ stated that, in general, the digestion of materials taken into a giant cell seems to go on just as it would in the individual cells which compose it. Unless the particle is insoluble, the digestion takes place by the action of intracellular enzymes. If the chemical substances are inert, they may remain in the cells for long periods.

Phagocytosis is a function of cell protoplasm, and the surface of a phagocyte is readily adjustable and easily permeable. It is not difficult to see how two such cells, either one of which is capable of incorporating a foreign body of a size nearly equal to itself, may under proper conditions fuse to form a cell with two nuclei.

The functions, in addition to phagocytosis, which have been attributed to giant cells, have been those of distributing infectious agents and of protection. Stschnastny³⁴¹ thought that giant cells were active agents in distributing tubercle bacilli, which they had phagocytosed in carrying them to new foci. Rous and Jones²⁰⁹ believed that, at times, cells of living tissues protected *Leishmania*, gonococci, *Bacillus leprae* and *Bacillus tuberculosis* against the destructive action of the body fluids. They demonstrated the protection of *Bacillus typhosus* in vitro by phagocytes. Giant cells probably have the same quality of protection

as single phagocytes. The fact that they completely engulf crystals and sharp irregular particles seems to indicate that they may serve also in protecting the more delicate tissue cells from injurious particles.

The ingestion of inert particles, such as glass and carbon, has not been satisfactorily explained. The assumption that they become coated with serum which serves as food for the phagocyte is not in itself satisfactory, since the cells themselves are in a medium of serum which surrounds them on all sides.

FATE OF GIANT CELLS

Comparatively few authors have discussed the fate of giant cells. Weigert³⁷² considered them necrotic from the beginning, and as resulting not only in their own destruction, but also in the death of the other cells in the area. Franchetti¹¹⁰ stated, on the other hand, that giant cells could remain in the tissues for long periods without either degenerating or changing back into connective tissue cells.

The final disposition of giant cells probably depends largely on the relative inactivity of the substances which brought about their formation. For instance, in a section in my possession, showing giant cells about silk sutures which had been placed in the dura at operation more than two years before the patient came to autopsy, the giant cells appear intact and healthy. This does not mean, of course, that they are the same giant cells originally formed at the site, but it does suggest that they are rather permanent structures. In tuberculous, anthracotic lungs, giant cells with circles of carbon pigment about the nuclei are commonly seen in the margins of healed, encapsulated caseous lesions. Sometimes they are the only nucleated cells in the area, which indicates that they have outlived the surrounding tissues. The presence of the phagocytosed pigment suggests that they are not recently formed cells, because most of the free pigment has disappeared from the area. Hence, it seems likely that giant cells may persist for long periods about foreign substances, and that they may even remain active, living cells until the degeneration or death of the other tissues in the region.

As for the fate of giant cells after the substances which attracted them are gone, the story may be different. Hektoen^{140,149} studied the breaking up of giant cells in a case of healing tuberculous meningitis, and found the giant cells fibrillating, splitting up and dividing into mononuclear cells. He followed up his observation with some experiments on the absorption of coagulated serum from the anterior chamber of the rabbit's eye, and concluded that in healing, nondegenerated tuberculous tissue, the multinucleated giant cells may, in part, disintegrate and undergo absorption, and in part form viable small cells. Cohen,⁶⁹ in his observations of cultures of turtle blood, not only witnessed the formation of giant cells by fusion, but also saw some of them break up into several smaller multinucleated giant cell masses.

THE OCCURRENCE OF GIANT CELLS

Giant cells may be found in any tissue of the body or in any kind of lesion which persists for more than the eight to fourteen days necessary for their development. Wherever there is an insoluble or slowly soluble substance too large to be ingested by a single cell, a giant cell will sooner or later appear. The substance may be extraneous material artificially or accidentally introduced, or it may be coagulated blood or exudate, or necrotic bodily tissue, the result of injury, of improper nourishment or of enzymatic action. The attempt to review their occurrence is limited to the more common and constant lesions in which they are found, and to a few unusual sites.

In Simple Granulation Tissues.—Lubarsch²²⁰ described the presence of giant cells in simple reparative granulations. He pointed out that they were there for the resorption of hemorrhage, hemoglobin pigment, coagulated bits of fibrin, injured elastic fibers and like matter. Langhans²¹² did his first work on phagocytosis by giant cells on the resorption of hemorrhage. Ssudakawitsch,²²³ Unna,²⁴⁶ Jores,¹⁷⁶ Hektoen¹⁵¹ and others described giant cells about elastic fibers. Mallory²⁴² stated that they may form about collagen fibers, and Goldzieher and Makai described them in the borders of infarcts and other like lesions. As examples of their occurrence in chronic inflammation, one may cite the presence of giant cells in the bronchioles in asthma, observed by Marchand;²⁵⁴ in bronchiolitis obliterans, witnessed by Vogel,²⁵⁴ and in organizing pneumonia, reported by Karsner and Myers.¹⁸⁰

In Areas of Degeneration, About Deposits and in Foci of Necrosis.—Giant cells have been described as occurring about both epithelial hyalin and connective tissue hyalin by Krückmann, Krause, Manasse and Mallory; and about areas of amyloid by Krückmann. Rhea (cited by Forbes¹⁰⁹) found them about degenerated colloid masses in the thyroid, and Wiesel²⁷⁹ in hyaline areas of the thymus. They are commonly found about deposits of calcium salts and about all kinds of crystals. C. Meyer,²⁶⁷ Manasse, Krückmann, LeCount²¹⁴ and others described giant cells filled with cholesterin crystals, or interpreted the clefts found in the cells as having contained cholesterin crystals prior to the passage of the tissues through alcohol. Manasse,²⁴⁵ Körner,¹⁹⁹ Friedrich and Kirchner¹⁸⁴ and Janssen (quoted by Grünert¹²⁸) reported giant cells in the so-called cholesteatomas of the ear, and Klemm¹⁹¹ found them in a large, cholesterin filled cyst of the omentum. They are also common about fatty acid cysts, as pointed out by Herxheimer,¹⁵⁵ Mallory²⁴² and others. In one of Klotz's class sets of sections, numerous giant cells are shown about bile pigment and fatty acids. I have frequently seen them in areas of fat necrosis of the pancreas and peritoneum. Weber²⁶⁶ produced them in subcutaneous fat by the injection of ether. They have been found about uric acid crystals and around

chalk stones in gout. I observed a remarkable case in which giant cells were numerous about the corpora amylacea in the prostate, and they are common about the similar structures in psammomas.

About Foreign Bodies.—Giant cells are found about all sorts of inert foreign bodies, as has been shown by the experimental work already cited. They were found early by Marchand and von Lesser²¹⁸ about catgut and silk sutures. They are found regularly about fatty, oily and paraffin masses injected for cosmetic purposes, and have been described as occurring in paraffinomas by Firkets¹⁰⁰ and others. I have seen them about several substances not yet mentioned, including gunpowder in burns, particles of carbon, glass, pieces of coal driven into the wounds of miners, and in a sinus which was under treatment with bismuth paste.

In Tuberculosis.—So much has already been said about giant cells in tuberculosis that little more than a summary need be added. Reviews of the early literature were made by Dürck,⁸⁶ Dürck and Oberndorfer,⁸⁷ Pertik,²⁸⁸ Paltauf²⁷⁷ and Köckel.¹⁰⁵ The predominant opinion about giant cells in tuberculosis at present is that they are identical with the foreign body giant cells which arise either from epithelioid cells or from wandering nongranular leukocytes. The stage of their formation presented in cells with two or three nuclei is the one about which the least seems to be known. If they are foreign body cells, the particles causing them to form must be extremely small and rarely acid-fast tubercle bacilli. Many who have accepted the fusion theory for larger cells have adhered to nuclear division for the smaller ones. Medlar's idea that giant cells are agglomerations of separate cells in caseous foci does not explain this stage of few nuclei, nor the final large globular cells. The Baumgarten-Weigert idea of giant cells as centers of necrosis may be correct in some instances, but cannot be applied universally. Bakacs' statement that giant cells indicate a progressive lesion, and their absence a healing one, will not hold. Isolated giant cells are often present in the borders of inactive, totally calcified, fully encapsulated lesions.

Stewart and Rhoads³³⁵ made an interesting observation with reference to the presence of giant cells in reactions of the skin to tuberculin. They explained their presence on the basis of foreign body giant cells gathered about small focal areas of necrosis, and not as a specific response to tuberculin. Weller³⁷⁶ pointed out that foreign body giant cells unassociated with products of tuberculous infection may occur by accident of position in tuberculous lesions. Warthin³⁶² described typical tubercle giant cells in placental tubercles.

In Syphilis.—Giant cells were described as occurring in gummas by Jacobson,¹⁶⁹ in 1877. They had been reported in syphilis previously by Baumgarten,^{26a} but were thought by him to be due to concurrent tuber-

culosis. Later, Baumgarten^{26b} reiterated his belief that giant cells were present in gummas only when tuberculosis also existed in the same lesion, and he pointed out that tuberculosis often coexisted with lymphosarcoma as well, which might account for their presence in sarcomas. Marchand²⁵⁰ disproved Baumgarten's claim by producing giant cells in all sorts of experimental lesions, and soon giant cells were reported in gummas of all parts of the body. Brissaud,⁴⁹ Malassez and Reclus²³⁸ and Schmaus and Sacki³¹⁸ reported them in syphilitic lesions of the brain, and Pick²⁹⁰ found them in a gumma of the spinal cord. Brodowsky,⁵² Thorel³⁴⁴ and Busse^{62, 63} reported them in gummas of the heart. Brodowsky⁵² thought they arose from angioplasts, and Busse believed they were metamorphosed muscle cells. Bruch found them in five cases of skin syphilis. Eisenberg saw them in a primary lesion, and Binder described them in congenital syphilis of the liver. Von Langenbeck²¹⁰ reported an interesting instance of coexistence of carcinoma and gumma in the tongue, and observed the presence in them of numerous giant cells. Herxheimer,¹⁵⁷ who reviewed the subject in 1908, pointed out the similarity between caseous and gummy necrosis; and said that if one accepted Weigert's theory of the formation of giant cells for tuberculosis, one might equally well apply it in syphilis. He concluded that giant cells in syphilis, including both those with centrally placed and those with peripheral nuclei, were due to the action of the specific virus.

It was formerly taught that a point in the differentiation of gummas from tubercles was the type of giant cell present. Lubarsch,²²⁹ in 1911, still adhered to this view. It will not hold generally, and has been dropped from the more recent American textbooks. Mallory²⁴²ⁱ stated that giant cells occur rarely in chancres and frequently in gummas, and that they are the same giant cells that form around elastic fibers, fat, its various products and fibrin. Karsner¹⁷⁸ stated that giant cells in gummas are of the same type as those in tuberculosis, but are less numerous. In gummas of bone, in which syphilitic giant cells and osteoclasts occur together, it is impossible to tell one from the other unless by their relations to other structures.

In Miscellaneous Granulomas.—Giant cells have been found in nearly all infectious granulomas. Duval and White⁶⁸ reported them in glanders, in which they thought that the cells developed by fragmentation of the nuclear chromatin. Mallory said that the giant cells of glanders varied somewhat in nuclear structure from the ordinary forms of giant cells. Eppinger⁹¹ and Ducor⁶⁵ reported that they observed them in actinomycosis, in which their presence was confirmed by Lubarsch^{229d} and Mallory. McCallum stated that they are rarely found in actinomycosis, and I have failed to find them in several cases outside the bone lesions.

Ricketts³⁰² reviewed the literature on oïdiomycosis and blastomycosis, and reported twelve new cases of oïdiomycosis. Giant cells were a constant observation in his cases; and his plates showing giant cells about the organisms are most beautiful. Hektoen,¹⁵⁰ Busse⁶² and others found them in blastomycosis; and I have had several cases, unreported, in which the giant cells filled with budding yeast forms furnished the differential point of diagnosis. Giant cells have been described as occurring in rhinoscleroma and mycosis fungoides by Lubarsch,^{220d} in Madura foot by Vincent,²⁴⁰ in paschachurda by Ssudakawitsch³³³ and in the tissues about abscesses due to *Sporotrichum schencki* by Hektoen and Perkins.¹⁵² Jadassohn¹⁷⁰ found them in erythema exudativum multiforme and nodosum, and Phillipson²⁸⁰ in erythema multiforme. Permar and Weil²⁸⁷ described giant cells as occurring in the skin lesions of a case of tularemia in man. An interesting and rather unusual lesion in which giant cells were a prominent feature was described by Warthin and Davis³⁰³ in their report of pseudotubercles of the skin due to cactus spines.

In the Vicinity of Animal Parasites in Body Tissues.—Animal parasites and their ova are sometimes the foreign bodies which lead to the development of giant cells. Paltauf,²⁷⁷ Wagenmann,³⁵⁵ Schroeder and Westphalen³²⁵ and others reported them about cysticerci. Lehne,²¹³ Krückmann,²⁰⁴ Vierordt²⁴⁸ and Guillebiau¹³¹ found them near the walls of echinococcus cysts. Mallory^{242x} said that they were common about encysted trichinae, and Hutchinson described them about the encysted ova of *Schistosoma haematobium* and *Schistosoma mansoni*. In some class material sent me some years ago by Hutchinson from Tanta, Egypt, I made a careful study of the formation of giant cells. I found great numbers of large giant cells both inside and around the empty shells of the ova and around the sides of them in rectal and bladder polypi. Mononuclear phagocytes appeared to have wandered into the small empty capsules through crevices in the walls, and later to have fused and formed large multinucleated giant cells.

In Giant Cell Granulomas of the Peritoneum.—Occasionally, surgeons, on opening the peritoneal cavity, find the peritoneal surfaces studded with small, more or less discrete nodules. The condition has frequently been mistaken for tuberculosis or general carcinomatosis. Several different conditions may give rise to the appearance. Hertzler¹⁵⁴ and others have applied the term pseudotuberculosis to it, and have described it in several forms: (1) a bacillary form, which apparently is not a definite entity; (2) a foreign body form, and (3) a form following the rupture of pseudomucinous cysts. I have not found any of the so-called bacillary forms, but I have had instances of the second and third forms. In one instance, I was sent a nodule by Dr. J. Alexander

for diagnosis by means of frozen sections. The nodule was from a patient supposed to have general carcinomatosis. I found a simple foreign body granuloma with most beautiful giant cells formed about bits of striped muscle and cellulose. The history revealed that the patient had been operated on two years before for a ruptured duodenal ulcer. Similar cases were reported by Marchand,²⁵⁰ Hanau,¹⁸⁶ Cooper,⁷⁸ Guthrie,¹³² C. Meyer²⁶⁷ and Ordway. Imbert, Cottalorda and Lagarde¹⁶⁶ reported similar lesions due to bits of lint and sponge left at operation. Coronini and Iatrou,⁷⁷ incising the stomachs of guinea-pigs, produced the condition experimentally.

A similar appearance may follow the organization of extensive fat necrosis. Here the giant cells form about small cystlike areas of degenerated fat and fatty acid crystals. I have had one such instance, and Herxheimer¹⁸⁵ reported a case in which the foci were calcified.

That the organization of pseudomucinous substances from ovarian cysts may take the form of foreign body granulomas has been shown by Eiger,⁸⁹ Frankel,¹¹¹ Werth,²⁷⁸ Gottschalk,¹²⁸ and Polano.²⁰³ This type of granuloma was reviewed by Merkel.²⁶²

Still another type may follow the organization of fatty substances and hairs discharged into the abdomen through the rupture of dermoid cysts. Instances of this type were reported by Krückmann²⁰⁴ and by Herzog.¹⁶⁰ The relatively common occurrence of these peritoneal conditions should not be forgotten by surgeons and pathologists associated with active surgical clinics.

In Inflammatory Lesions of the Bones and the Joints.—Since the osteoclast is in all probability a foreign body giant cell in a special environment, and is a normal constituent of all embryonic and adult bones, it almost goes without saying that they are found in every type of lesion of the bone. They are important in the embryonic development of bones (Keibel and Mall,¹⁸⁹) in the healing of injuries and fractures, taking up not only bone salts but blood pigment as well, and in the resorption of calluses and of bony excrescences. That they do not necessarily have their origin in bone tissue is shown by their appearance about transplants into subcutaneous tissues of dead bone and polished ivory.

McCallum,^{283d} Mallory^{243j} and Karsner¹⁷⁸ described giant cells as constant observations in acute and chronic osteomyelitis, in infectious granulomas of bone, in rickets, in osteogenesis imperfecta and allied conditions, in osteomalacea, in osteitis deformans of Paget and in other conditions of the bone. Giant cells were found in arthritis deformans by Nichols and Richardson,²⁷² and they are usually present in all other types of arthritis. They are common in pyorrhea pockets about the teeth, and material obtained in curetting tooth sockets.

THE GIANT CELLS IN TUMORS

The giant cells in tumors have been known since the work of Müller²⁷¹ in 1838. The confusion which existed concerning the origin and nature of giant cells generally was largely due to the recognition that the giant cells in tumors often differed widely from those in tuberculosis and in foreign body granulomas. Rustizky³¹¹ and others reported giant cells resembling osteoclasts in sarcomas of the bone, and the term "giant cell sarcoma" came into use. Lubarsch³²⁶ stated that among the earlier textbooks of pathology, Thoma's was the only one which described a giant cell tumor outside the bone, and his exception was that of a giant cell sarcoma of the breast. The mistake which was made was that of considering all tumors containing giant cells as being identical in origin. C. Meyer²⁶⁷ and Ziegler³³⁹ later pointed out the wide distribution of giant cells in tumors, and explained them on the basis of foreign body giant cells.

Krückmann²⁰⁴ undertook to determine whether or not all giant cells were the same, regardless of the tissue in which they might occur. He compared those in tuberculosis with those found around foreign bodies, about parasites, in sarcomas and in epithelial tumors; and decided that they were not all alike, but that they came from several different sources. He concluded that many of them could be accounted for on a foreign body giant cell basis, and that they were formed about such substances as pigment, glycogen, amyloid and possibly hyalin. He cited Lubarsch's instructive case of a periosteal sarcoma of the forearm, which proved that some of the giant cells could be entirely independent of the essential cells of a tumor. The primary growth contained only spindle cells; the first recurrence was made up of spindle cells and foreign body giant cells together; while at autopsy many of the spindle cells were multinucleated, and comparatively few large giant cells of the type found round a foreign body were present. Krückmann, in discussing this case, said that, in the last recurrence, two kinds of giant cells were present: those which were related to osteoclasts and belonged to bone, and those which were tumor giant cells and which metastasized to the secondary sites.

Stroebe³⁴⁰ believed that tumor giant cells were foreign body giant cells which arose from tumor cells, partly by nuclear division and partly by fusion. Klebs¹⁸⁷ not only found multiple mitoses in tumor cells, but such large ones that he called them "giant mitoses." Manz²⁴⁷ took the stand that the giant cells in sarcomas were of two kinds: one kind arose from the rapid proliferation of true tumor cells and contained many nuclei; the other arose from the degeneration of tumor cells and the fusion of degenerated cells. Rindfleisch³⁰⁴ believed that the giant cells in bony tumors were osteoclasts released by bony resorption. Malassez²³⁷ traced them to proliferated endothelium, while Borst⁴⁷ and Ziegler³³⁹

thought they had multiple origins. Mallory²⁴¹ advanced the explanation that the giant cells in tumors were of at least two types. One was a true tumor giant cell originating from tumor cells by multiple mitosis due to rapid growth, and varying with the type of tumor concerned. The other was a foreign body giant cell formed by the fusion of endothelial leukocytes. The latter cells were not tumor cells, although the tumors which contained them were called "giant cell sarcomas." He said that such sarcomas should be classified according to the nature and type of the essential cell from which they arose, and that the use of the term "giant cell sarcoma" should be discontinued. It has been my practice, in instructing students in the subject of giant cell tumors to advise them to disregard the giant cells and study only those cells which unquestionably are tumor cells.

Occurrence of Giant Cells in Tumors of the Bone.—Until recently, the understanding and interpretation of tumors of the bone was in a greatly confused state. Since almost all giant cell tumors of bone were classed together, it was difficult to reconcile the great variations in malignancy which were constantly encountered. The occurrence of giant cell tumor of the bone in man was reviewed by M. B. Schmidt,³²⁰ and its occurrence in animals by Casper.⁶⁷ In early reports, Rustizky³¹¹ and Hanseemann¹³⁷ appreciated that in myelomas there were two kinds of giant cells: the osteoclasts, and the megakaryocytes, or giant nuclear cells. Mallory's²⁴¹ article on giant cell tumors threw considerable light on the question, and the reports of Bloodgood³⁹⁻⁴¹ demonstrated that there were essential differences in so-called giant sarcomas of bone.

The present interpretation is largely due to the work of Codman,⁶⁸ who established the "Registry of Bone Sarcomas," and to the "Registry Committee of the American College of Surgeons," to which Codman's collection was given. Ewing^{96a} was closely associated with the work of the registry, but did not accept Codman's classification in its entirety. Kolodny¹⁹⁸ restudied the cases and made still another classification. My review follows the original classification, but, as it has to do with the tumors only so far as the various types contain giant cells, a particular text is not followed.

Classification of Tumors: 1. *Metastatic Tumors Primary in Tissues Other Than Bone:* Any metastatic tumor which destroys bone, whether it is epithelial or mesoblastic in nature, is likely to contain two kinds of giant cells: those multinucleated forms which originate from tumor cells; and those which are associated with the resorption of bone, and which have been interpreted either as ordinary foreign body giant cells or as a specific form of giant cell, the osteoclast.

2. **Periosteal Fibrosarcoma:** This class includes tumors which morphologically are fibrosarcomas or fibroblastomas and which lie next to the external surface of the bone, but do not invade it. The cells are spindle shaped and may be multinucleated, and they may form fibrils. They may also contain foreign body giant cells about areas of necrosis and hemorrhage, or about elastic or collagen fibrils.

3. **Osteogenic Sarcoma or True Bone Sarcoma:** This group is believed to come from the cells from which embryonic bone develops, and so may contain fibrous, myxomatous, cartilaginous and bony or osteoid portions as well as completely undifferentiated cells. The tumors may be periosteal, subperiosteal or medullary in origin; and they may tend to form bony trabeculae, may tend to be sclerosed compact masses or may grow rapidly and take on a loose, spongy structure called the telangiectatic form. All variations of fibrous, myxomatous, cartilaginous or osseous cells may be present; or the general structure may tend to differentiate chiefly into a fibrosarcoma, a myxosarcoma, a chondrosarcoma, an osteogenetic sarcoma, an osteoidsarcoma or the rapidly growing undifferentiated cell form. In any of these types may be found true tumor giant cells, respectively of the fibroblastic, myxoblastic, chondroblastic and osteoblastic forms. Such cells may contain large vacuolated or globular single nuclei with one or several nucleoli, and may be hyperchromatic, with or without the figures of nuclear division; or they may be multinucleated, having anywhere from two to a dozen or more separate nuclei. The tumor giant cells tend to differentiate, so far as their shape and intercellular substance is concerned, like the cells from which they come. Therefore, the fibroblastic cells are spindle shaped, with more or less spindle shaped nuclei, and often form fibroglia (Mallory²⁴¹) and collagen, and do not tend to shrink away from the surrounding cells on fixation. Myxoblastic cells are probably modified fibroblasts and resemble them save for the serous or gelatinous intercellular substances. The chondroblastic and osteoblastic giant forms differentiate as irregularly round or oval cells, which shrink away more or less from the intercellular substances. The chondroblastic forms are generally embedded in a more or less definite chondromucinous or cartilaginous ground substance. The multinucleated osteoblasts tend to arrange themselves along the borders of osteoid trabeculae with fibrous tissue on the opposite side. They may be interspersed with single cells of the same type, and may occur in single layers or pile up in concentrated masses.

Mallory describes the other type of giant cells, which are larger, contain great numbers of nuclei and tend to retract from the surrounding cells on fixation, as foreign body giant cells formed from fused endothelial leukocytes. Ewing states that giant cells are found in all forms of

osteogenic sarcomas as a result of the overgrowth or fusion of tumor cells, and may be large or small with single or multilobar nuclei. They are found in the walls of the cysts, along the bony sinuses and about extravasated blood. The presence of great numbers of these foreign body giant cells may lead to an erroneous diagnosis of a benign giant cell tumor.

4. Inflammatory Conditions: Codman placed inflammatory conditions near the center of the list, because exuberant callus and osteogenic sarcomas are similar in their histology, and because such lesions as osteitis fibrosa and bone cysts are interpreted by some pathologists as tumors and by others as inflammatory lesions. Apparently, the only type of giant cell found in these lesions is of the foreign body or osteoclastic variety.

5. Benign Giant Cell Tumor: This term was suggested by Bloodgood to replace the older one of "giant cell sarcoma," and was accepted by the registry, because a clear tumor of this group has not been found to metastasize. According to Mallory, these tumors are inflammatory, and were wrongly termed "giant cell sarcomas," because the giant cells are not tumor cells but are all foreign body giant cells. Ewing apparently did not wholly agree, because he offered the synonymous name of "osteoclastoma" for the members of this group. Bloodgood showed that this group, from the clinical standpoint, is not of a malignant nature.

6. Angioma of the Bone: This tumor is usually benign and frequently contains foreign body giant cells in the stroma and about hemorrhagic areas outside the vessel lined spaces.

7. Ewing's Tumor: Kolodny stated that Ewing's tumor is a characteristic tumor which varies from osteogenic sarcoma and frequently is multiple. The type cell is small and polyhedral, having round, oval or slightly elongated nuclei and scant, clear, stainless cytoplasm. The nucleus stains palely and contains scattered granules of chromaffin. The nuclei are not easily seen. While mitosis may be abundant, true tumor giant cells or multinucleated cells are not found. It often assumes the form of the old perithelial angiosarcoma. Ewing believed that it originates from the perivascular endothelium, and called it an endothelial myeloma.

8. Myeloma: Myelomas constitute a group of central tumors not producing bone and made up of cells which resemble the cells of the myelocyte series and which are usually multiple. The exact nature of the cells is not known. According to Mallory, they are not myeloblastic, and by exclusion he suggested the possibility of their origin from erythroblasts or megakaryocytes. The cells are of medium size and often compressed into polygonal forms. Some examples resemble plasma cells. These tumors are often associated with bone resorption

and multiple fractures. Myelomas have also been called plasmocytoma, lymphocytoma, myelocytoma and erythroblastoma. The tumor cells are often multinucleated (Kolodny¹⁰⁸). It is possible to get several varieties of giant cell forms: (a) the multinucleated tumor cells, (b) the foreign body osteoclastic forms associated with bone resorption and fractures and (c) megakaryocytes, which are present in the bone marrow, the common site of the myelomas.

In addition to the bone tumors included in Codman's classification, there are two other examples which involve bone and other tissues, but which are not characteristic lesions of bone.

(a) *Epulis*: It was formerly taught that the epulis was an unusual form of giant cell sarcoma affecting the jaws, and known not to produce metastases. At present, the epulis is considered variously as being an inflammatory lesion characterized by the presence of foreign body giant cells, as a fibroma, or benign giant cell tumor, or as an osteoclastoma. In any case, it is not malignant, and the contained giant cells are of the foreign body type.

(b) *Xanthoma*: Giant cells are nearly always found in xanthomas and xanthosarcomas. There are two kinds of xanthomas (Lubarsch²²⁷): those connected with the eyelids; and those found in joints, tendons, bursa and allied places. The term is not a good one, as it refers to the characteristic appearance of the tumor, not to its true nature. Xanthosarcomas include hemangiomas, endotheliomas, sarcomas and even carcinomas. Garrett¹¹⁸ reported on a study of 196 tumors diagnosed as xanthosarcoma, and stated that foreign body giant cells may or may not be present, and when present are without particular significance so far as prognosis is concerned. When present, they are usually filled with phagocytosed pigment.

There is probably no other group of lesions in which it is so important to be able to interpret the giant cells as it is in the bone tumors. The prognosis may depend on the differentiation of the kinds found.

Giant Cells in Tumors Other Than Tumors of the Bone.—Practically all benign tumors undergo degeneration in part or produce dense fibrillar structures which lead to the formation of foreign body giant cells. These cells are practically all large phagocytes and appear to come from wandering phagocytes by fusion, nuclear proliferation or both.

In fibromas, the cells are present about hyalin, pigment, collagen and necrotic foci.

In lipomas, giant cells form in foci of necrosis or in deposits of fatty acid crystals. In fibroids, or leiomyomas, they are common in areas of liquefaction, necrosis and calcification. In endotheliomas, they are seen about small extravasations of blood. In dural endotheliomas (the

arachnoid-fibroblastoma of Mallory), foreign body giant cells are common about bits of hyalin which are included in the whorls.

In fibrosarcomas, leiomyosarcomas and melanosarcomas, both true tumor cells and foreign body giant cells are likely to be found.

Psammmoma, like xanthoma, is not a tumor characterized by a specific type of cell; the term is applied to any tumor containing sandlike granules. Similar structures occur in various forms, and are found in carcinomas, in dural endotheliomas and in the dura along the longitudinal sinus of the skull. In the dural growths, the sandlike material is calcified hyalin (Mallory). Psammomas usually contain numbers of giant cells of the foreign body type.

Rhabdomyomas and rhabdomyosarcomas contain the most beautiful of all tissue giant cells. Most of them are true tumor cells and are large, irregular embryonic muscle cells. They vary greatly in size and shape, may have single or multiple nuclei, nuclear figures, multiple nucleoli and varying degrees of hyperchromatosis. Those arising from heart muscle usually have each a single nucleus with beaded, radiating striae filling the cytoplasm. In those from striped muscle there are often spheres, rhomboids, ovoids, racket shaped cells and slender ladder-like structures, which are prolongations of cells containing crossed striae. Foreign body giant cells may also occur in these tumors, but, as a rule, they may easily be differentiated. If not, they can be specifically stained by several stains, of which Mallory's phosphotungstic-acid-hematoxylin is, perhaps, the best.

Ribbert³⁰¹ interpreted the muscle giant cells of rhabdomyomas as of congenital origin rather than as metaplastic products, because of their resemblance to embryonic muscle and on account of the occurrence of the tumors in early life and in association with mixed tumors.

In 1872, Langhans reported giant cells in malignant lymphoblastomas, which he thought were identical with those of tuberculosis. Askanazy¹⁴ and Paltauf²⁷⁹ also found them in lymphosarcomas. From the time that Hodgkin¹⁶⁸ described seven clinical cases of bilateral symmetrical enlargement of the glands of the neck, a lively controversy has been waged between the school which classifies the disease as granuloma and those which believe it to be a form of lymphoblastic tumor. Regardless of the reader's convictions in the matter, in both Hodgkin's disease and lymphoblastic tumors two similar types of giant cells are usually found. One of these is characteristic of the growth in both conditions, although much more easily demonstrated in Hodgkin's disease. It is often spoken of as the "Sternberg Cell"³³⁴ or as the "Dorothy Reed Cell."²⁹⁸ According to Reed, the cell is a transformation of an epithelioid cell which, in turn, has come from the endothelium lining the lymph sinuses or cover-

ing the reticulum of the germ center. According to Mallory,²⁴² it is a lymphoblast. Reed describes it as a large epithelioid type of cell with a vesicular nucleus or with several nuclei, generally of a bean shape, and having prominent nucleoli. The nuclei may be in the periphery or arranged in a central clump. She did not observe mitoses in them. The lymphoblast of Mallory is the same cell, and often contains numerous typical and atypical mitotic figures. Reed described another type of giant cell with small peripherally arranged nuclei, which she interpreted as Langhans' giant cell. Mallory also stated that Hodgkin's disease commonly contains foreign body giant cells. Apparently, the two types are found associated constantly in Hodgkin's disease and tumors of the lymphoblast group, but are wholly unrelated so far as origin is concerned.

Foreign body giant cells in chloroma have been described by Billroth,³⁵ and in Gaucher's disease of the spleen by Waugh and MacIntosh.²⁶⁵

Gliomas and gliosarcomas frequently contain two types of giant cells: one is a multinucleated glial cell (Bailey and Cushing²¹), which is specific for glial tumors; the other is not distinguishable from the foreign body giant cell. It most likely originates from phagocytic cells of the blood or vascular tissues, and is of endothelial nature, but, as was mentioned under the discussion of varieties of giant cells, they have been attributed to wandering glial phagocytes of the ameboid class of Alzheimer, and this possibility has not been definitely excluded.

Epithelial Tumors.—Two kinds of giant cells have been described as occurring in epithelial tumors: those which come from epithelial tumor cells, and those which are foreign body giant cells similar in all respects to foreign body giant cells elsewhere in the body. Krause²⁰² was one of the first to study giant cells in carcinomas. He found them in the centers of the epithelial pearls and in the margins of epithelial islands in ten of seventy epitheliomas which he reported. He thought they formed through the compression and fusion of tumor cells. Krückmann²⁰⁴ found giant cells in sebaceous adenomas, dermoid cysts and epitheliomas, and concluded that they are snared-off bits of tumor epithelium. Orth²⁷⁵ found them in the stroma about cancer nests in association with calcium salts, and explained them on a foreign body giant cell basis. Lubarsch²²⁶ stated that foreign body giant cells are common in cancers and are present about areas of cornified epithelium, cell detritus, cholesterin and deposits of calcium. Apparently all of these authors were dealing with foreign body giant cells, though they were not agreed as to their origins. C. Lubarsch²²⁴ reported typical foreign body giant cells in a hypernephroma. They are common in adenomas of the meibomian glands (Weis³⁷⁴ and Zielonko³⁹⁹).

The term "carcinoma gigantocellulare" has sometimes been applied to carcinomas, but it should be reserved for tumors composed of large syncytial masses of tumor cells, and should not be used in connection with carcinomas in which only foreign body giant cells are found. Babes²⁰ reported a carcinoma of the liver, which was composed of large multinuclear syncytial-like cell masses in which great numbers of mitoses were present. Goldzieher and Makai¹²⁵ encountered a large multinuclear cell parenchymatous tumor to which they applied the term "gigantocellulare." Rowen and Mallory³¹⁰ reported a similar tumor, and I have seen two others within the last year. Giant epithelial cell tumors sometimes occur in the cervix, breast, esophagus and intestinal tract. Tumors composed of large syncytial epithelial masses have been reported in chordomas by Mallory, and in chorionepitheliomas of the uterus and testis by Aschoff,¹¹ Marchand²⁵³ and others. Cells of the latter types are easily differentiated from foreign body giant cells.

CRITICAL CONCLUSIONS

1. The multinuclear giant cells of the body may be divided into two groups: (a) specific tissue cells, which include megakaryocytes, muscle repair clubs, epithelial syncytia of parenchymatous and placental origin, and true multinucleated type cells from various tumors; (b) foreign body giant cells, which include the large multinuclear phagocytic cells occurring about pigment, inorganic salts, crystals and foreign bodies; the Langhans cell of tuberculosis, and the similar foreign body cells of syphilis, leprosy and other granulomas; the foreign body giant cells of tumors, and the osteoclasts.

2. The foreign body giant cells either are identical or are all closely related to each other, and probably are all derived from mononuclear phagocytes.

3. The participation in the formation of foreign body giant cells by lymphocytes has not yet been definitely proved, although phagocytosed lymphocytes within them are not uncommonly seen.

4. The question regarding nuclear multiplication and fusion is still unsettled. Fusion has been observed in tissue cultures, and some of the histologic pictures are difficult of interpretation in any other way; but nuclear proliferation also occurs in tissue cultures, and occasionally mitoses have been observed in foreign body giant cells. It is probable that either method of increasing the number of nuclei may occur.

5. The function of foreign body giant cells is undoubtedly one of phagocytosis and defense. It is possible that giant cells may protect tubercle bacilli mechanically for a time, and even distribute them within a limited radius.

6. Foreign body giant cells are so widely distributed in all types of pathologic lesions that when they are encountered in a section, the pathologist should rule out other possibilities before making the diagnosis of tuberculosis.

7. The giant cell of tuberculosis is a type of foreign body giant cell, and cannot be differentiated from the giant cells of other granulomas except by the demonstration of tubercle bacilli.

8. The diagnosis of giant cell sarcoma should not be applied to a tumor when foreign body giant cells are the only kind of multinucleated cells present. The effort of the pathologist should instead be directed toward interpreting the type of the essential cell composing the new growth.

9. The differentiation between foreign body giant cells and true tumor giant cells is usually not difficult if the points already cited are kept in mind.

10. The presence of a mitotic figure in a giant cell when found in a new growth usually indicates that the cell which contains it is a true tumor giant cell and that the tumor itself is malignant.

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Notes and News

University News, Promotions, Resignations and Appointments.—Frederick R. Weedon, formerly of the department of pathology of the University of Chicago, has been appointed pathologist of the Macon Hospital, Macon, Ga.

An assistant professorship of pathology in the college of medicine of the University of Tennessee, Memphis, is vacant.

John Hays Bailey has been appointed Huesmann fellow at the Riley Hospital for Children of the Indiana University, Indianapolis.

At Stanford University, Albert Paul Krueger has been promoted to assistant professor of bacteriology.

Eric D'Ath has been made professor of pathology in the University of Otago, New Zealand.

Ralph W. Webster has been appointed chemist to the coroner's office of Cook County (Chicago) in the place of William D. McNally, resigned.

Robert L. Benson has resigned as head of the department of pathology in the University of Oregon Medical School, Portland, Ore., and Frank R. Menne has been appointed in his place. Dr. Benson will remain connected with the school nominally as clinical professor of pathology.

H. Douglas Symmers has been appointed general director and Armin V. St. George assistant director of the hospital laboratories of New York City.

Guiseppe Caronia of the Institute of Epidemiology, Naples, is to work for a year on measles and scarlet fever at the Hooper Foundation for Medical Research of the University of California, San Francisco.

Robert Hegner, professor of protozoology in Johns Hopkins University, is to serve for one year as visiting professor in the University of the Philippines, Manila.

Carl Koller, New York, has received the Kussmaul medal of Heidelberg University for his work in Vienna in 1884 on cocaine as a local anesthetic in ophthalmology.

The annual John Scott medal of the city of Philadelphia has been awarded to Herbert M. Evans, professor of anatomy in the University of California, for his work on the antisterility vitamin E.

Alfred Maurice Wakeman of the Yale Medical School died at the age of 32, on March 2, 1929, at Lagos, Africa, while investigating yellow fever.

Maurice Letulle, professor of pathologic anatomy in the Faculté de Paris and a member of the Académie française, died at the age of 76.

Erwin Christeller, professor of pathologic anatomy in Berlin, died recently.

Eugene Latreille, professor of pathology in the Université de Montréal, died recently.

Registry of Technicians.—The American Society of Clinical Pathologists has organized a registry for laboratory technicians. Certificates are issued to properly qualified persons. Schools and laboratories that give courses for training technicians are to be inspected and standardized. The registry also will conduct a placement bureau for registered technicians.

Meeting of Association of American Physicians.—The fourth annual meeting of the Association of American Physicians will be held at the Hotel Traymore, Atlantic City, N. J., May 7 and 8, 1929.

News of Societies.—At the recent annual meetings in Chicago, the American Association of Pathologists and Bacteriologists elected officers as follows: president, George H. Whipple; vice president, G. R. Callender; treasurer, F. B. Mallory; secretary, Howard T. Karsner; member of the council, E. T. Bell.

The American Association of Immunologists elected the following officers: president, Oswald T. Avery; secretary-treasurer, Arthur F. Coca, and councilor, S. Bayne-Jones.

The International Society of Microbiology will hold an international congress in Paris in September, 1929.

The Seventh International Congress of the History of Medicine will meet in Rome in September, 1930. The president is Dr. Pietro Capparoni, 108 Via Pozzetto, Rome.

The next International Physiological Congress will meet in Boston, Aug. 19-23, 1929, under the presidency of William H. Howell. Walter B. Cannon, Harvard Medical School, has charge of the arrangements.

The next annual meeting of the American Society of Clinical Pathologists convenes in Portland, Ore., July 5, 6 and 8, 1929.

The twenty-second annual meeting of the American and Canadian Section of the International Association of Medical Museums was held in Chicago on March 27. The following officers were elected: president, H. E. Robertson; vice president, G. R. Callender; secretary, Maud E. Abbott.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

CALCIUM AND PHOSPHOROUS METABOLISM OF EPILEPTIC CHILDREN RECEIVING A KETOGENIC DIET. MARTHA NELSON, *Am. J. Dis. Child.* **36**:716, 1928.

Determinations were made of the calcium and phosphorus intake and output of three epileptic children receiving a ketogenic diet. In each instance, the output of calcium and phosphorus exceeded the intake. There was a shift of the major excretion from the stool to the urine, the increase of urinary calcium being proportionally greater than the increase of urinary phosphorus. The values for the calcium and phosphorus of the blood during fasting were within normal limits.

AUTHOR'S SUMMARY.

THE EFFECT OF THE LEVEL OF OVARIAN ACTIVITY ON THE METABOLISM OF GALACTOSE. ALLAN WINTER ROWE and MARY MCGUINNESS, *Am. J. Obst. & Gynec.* **16**:687, 1928.

Rowe and McGuinness demonstrated that the limits of assimilation of galactose vary with the functional activity of the ovaries. In prepubertal years the average galactose tolerance was 20 Gm. There was a gradual increase with the onset of puberty, and the highest tolerance, 40 Gm., was reached during maturity. When the menses ceased there was a moderate decrease in tolerance, but when the ovaries were removed the tolerance was decreased to the prepubertal level.

A. J. KOBAK.

ARTIFICIAL PRODUCTION OF STERILITY WITH SPECIAL REFERENCE TO EXPERIMENTAL TEMPORARY STERILITY BIOLOGICALLY INDUCED IN THE FEMALE. JULIUS JARCHO, *Am. J. Obst. & Gynec.* **16**:813, 1928.

Jarcho adduces experimentally that rabbits can be artificially rendered temporarily sterile by injecting spermatozoa obtained from rabbits, guinea-pigs and sheep. The rabbits were divided into three series: those injected with (1) live spermatozoa washed and unwashed; (2) spermatozoa killed by formalin, and (3) spermatozoa destroyed and disintegrated by grinding in a mortar containing sea sand. From the latter, emulsions were made with sodium chloride or alcohol. The spermatozoa were also disintegrated by sodium hydroxide which was afterward neutralized with normal hydrochloric acid. The solutions of emulsified spermatozoa were first passed through a Berkefeld filter before using. The spermatozoa in all series were injected hypodermically or intramuscularly in doses of 30,000,000 per cubic centimeter in the series in which the sperms were intact. The behavior of the rabbits thus inoculated was normal. Spermatotoxicity of the serum was discussed but was found to be inconstant. It was suggested that the toxic agent was in the vaginal secretions and the spermatozoa were probably destroyed in the vagina after normal copulation.

A. J. KOBAK.

PHYSICAL DEVELOPMENT AND THE EXCRETION OF CREATINE AND CREATININE BY WOMEN. P. HODGSON and H. B. LEWIS, *Am. J. Physiol.* **87**:288, 1928.

In a number of women with unusual physical development—professional students in courses in physical education—creatinine coefficients of the same order as those of men were found. The excretion of creatine was found with a frequency similar to that usual in women, indicating that the creatinuria of the female sex is probably not related to differences in muscular development in men and women.

H. E. EGGERS.

THE DEVELOPMENT OF SECONDARY SEX CHARACTERS IN CAPONS BY INJECTIONS OF EXTRACTS OF BULL TESTES. L. C. MCGEE, M. JUHN and L. V. DOMM, *Am. J. Physiol.* **87**:406, 1928.

The injection of a benzene-soluble lipin fraction obtained from bulls' testicles caused in capons a growth of comb, wattles and ear lobes. The amounts injected were from 150 to 500 Gm. of fresh testicular material. Individual variation was observed, but the reaction was sufficiently constant to serve as a roughly quantitative method of assay of the lipin preparation. Partial purification of the material was effected by fractional precipitation by methyl alcohol, ethyl alcohol and acetone, or by extraction with liquid ammonia. The activity of the material was only partly affected by boiling with alcoholic sodium hydroxide for nine hours, but was lost completely after boiling for eighteen hours.

H. E. EGGERS.

THE EFFECTS OF LIPOID EXTRACTS OF BULL TESTES ON CASTRATED GUINEA-PIGS. C. R. MOORE and L. C. MCGEE, *Am. J. Physiol.* **87**:436, 1928.

Using benzene-soluble lipid extracts of bull testes, it was found that the injection of these into castrated guinea-pigs gave effects similar to those of the intact living testicle. As a measure of this effectiveness, the rate of persistence of living spermatozoa in the epididymis was selected. In the absence of a testicular hormone, these persist for twenty-three days. In the animals receiving the injections, they persisted for from thirty-five to fifty-four days, while their persistence in uncastrated normal animals is sixty-five days.

H. E. EGGERS.

DISTRIBUTION OF TESTICULAR COMB GROWTH STIMULATING PRINCIPLE IN TISSUES. T. F. GALLAGHER, *Am. J. Physiol.* **87**:447, 1928.

A study of the possible sources of the lipoidal hormone of bull testis showed that it was absent in all other tissues except the epididymis, where it was present in lesser amount than in the testis. It was not found in whole beef ovary.

H. E. EGGERS.

AN IMPROVED METHOD FOR THE DETERMINATION OF CARDIAC OUTPUT IN MAN BY MEANS OF ETHYL IODIDE. I. STARR, JR. and C. J. GAMBLE, *Am. J. Physiol.* **87**:450, 1928.

The authors found it impossible to estimate correctly the ethyl iodide content of arterial blood from the content of this substance in the alveolar air, and of venous blood by the content in rebreathed air. They report a series of experiments by which a method is developed for the determination of the rate of the blood flow through the lungs, which requires no active cooperation of the subject.

H. E. EGGERS.

THE RESPIRATORY QUOTIENT AND BASAL METABOLIC RATE FOLLOWING REMOVAL OF THE LIVER AND INJECTION OF GLUCOSE. F. C. MANN and W. M. BOOTHBY, *Am. J. Physiol.* **87**:486, 1928.

Using trained dogs, a series of observations of gaseous metabolism was made before and after removal of the liver and before and after the injection of dextrose. While the respiratory quotient increased immediately after removal of the liver, the total production of heat was not directly affected by the total loss of hepatic tissue; dextrose had a greater specific dynamic action in dehepatized than in normal animals.

H. E. EGGERS.

THE EFFECT OF REMOVAL OF THE LIVER ON THE SPECIFIC DYNAMIC ACTION OF AMINO-ACIDS ADMINISTERED INTRAVENOUSLY. C. M. WILHELMJ, J. L. BOLLMAN and F. C. MANN, *Am. J. Physiol.* **87**:497, 1928.

Following the two operations (reverse Eck fistula with ligation of the vena cava, and later ligation of the portal vein) preceding removal of the liver in

dogs, there was found to be no alteration of the specific dynamic action of amino-acids injected intravenously. Following removal of the liver there was no evident change of the consumption of oxygen, but the respiratory quotient showed spontaneous and persistent elevation. The intravenous injection of amino-acids into these animals failed to produce an increased consumption of oxygen, but further elevated the respiratory quotient. A specific dynamic effect of the amino-acids failed in the same way with the blood sugar content within normal limits. The experiments indicate that the specific dynamic action of the amino-acids is not the result of direct stimulation by the presence of unchanged amino-acids within the tissues.

H. E. EGGERS.

PHYSIOLOGICAL ACTIVITY AND THE MANOILOV REACTION. O RIDDLE and W. H. REINHART, *Am. J. Physiol.* **87**:517, 1928.

In a study of the Manoilov reaction (the modification of the oxidation of dahlia by body fluids), it was found that the test was really an expression of the metabolic activity of the part represented by the fluid, and that to the extent that it serves as a sex-reaction, the test is based on the relation of metabolism to sex.

H. E. EGGERS.

PRODUCTION OF RENAL INJURY IN THE WHITE RAT BY THE PROTEIN OF THE DIET. L. H. NEWBURGH and A. C. CURTIS, *Arch. Int. Med.* **42**:801, 1928.

Young white rats were given adequate diets containing an excess of proteins for varying lengths of time to more than 500 days. Evidence of injury of the kidneys was found in the urinary casts and albumin, and in histologic sections. Excess of casein caused but little nephropathy, even in amounts of 75 per cent given for more than a year. Beef muscle proteins in amounts greater than 31 per cent of the diet gave casts, albumin and degenerative changes of the tubules and glomeruli with fibrosis. Seventy-five per cent of beef liver caused marked granulation of the kidneys in 300 days. It is believed that the amino-acid make-up of a protein determines its nephrotoxic action.

HAMILTON R. FISHBACK.

EXPERIMENTAL UREMIA. M. H. STREICHER, *Arch. Int. Med.* **42**:835, 1928.

A ten to twenty per cent solution of urea was injected intravenously into dogs, at the rate of 200 cc. daily for three days. In about 40 per cent of the dogs a picture resembling uremic coma was produced after injecting 200 per cent of urea solution, while practically all the animals became comatose after the second or third injection of 200 cc. Urea in the blood increased to 700 mg. after the third injection. There was an increase in blood calcium and a decrease in potassium, so that the potassium-calcium ratio fell below one. The carbon dioxide was constantly decreased as in human uremic acidosis, and the blood pressure rose as high as 220 mm. of mercury. The intestines showed marked hyperemia but no ulceration.

HAMILTON R. FISHBACK.

THE UREA TOLERANCE TEST. S. E. KING, *Arch. Int. Med.* **42**:877, 1928.

Kidney function was studied by repeated estimation of the blood urea after giving by mouth 1 Gm. of urea for each 10 pounds (4535 Gm.) of body weight. Standard conditions were adopted as to fluid and food intake and rest in bed. In all normal subjects the blood urea had dropped to within 2 mg. of the rest level after fourteen hours. In a series of cases with definite renal impairment the average elevation of the blood urea nitrogen in two hours was 15.9 mg., as compared with a normal amount of 10.5 mg. After fourteen hours the blood urea nitrogen averaged 10.3 mg. above the rest level. In over half these cases the urine was in excess of the 750 cc. set as a maximum normal amount.

HAMILTON R. FISHBACK.

THE EFFECT OF PARATHYROID EXTRACT ON EDEMA. A. CANTAROW and B. GORDON, Arch. Int. Med. 42:939, 1928.

The blister method for studying the permeability of capillaries and the intra-dermal test with salt solution were carried out on patients with tuberculosis, nephritis and cardiac conditions. Variation of the calcium content of the blood was effected by the injection of parathyroid extract. The appearance of the blister was delayed and the rate of accumulation of blister fluid was decreased after the administration of parathyroid extract. The permeability ratio gave contradictory results in the same cases. It is considered that the chief factor in the production of inflammatory edema is increased permeability of the walls of the capillaries. The duration of the wheal after the injection of salt solution into the skin of patients with nephritis and cardiac conditions was lengthened in every case after the injection of parathyroid extract. The increase of available calcium seemed to lessen the capacity of tissue colloids for hydration, probably through the replacement of sodium ions by calcium.

HAMILTON R. FISHBACK.

STUDIES ON THE METABOLISM OF ESKIMOS. P. HEINBECKER, J. Biol. Chem. 80:461, 1928.

A brief account of the diet of Polar and Baffin Island Eskimos is given. By means of glucose tolerance curves it is shown that these people have a high tolerance for carbohydrate. Following a period of fasting this tolerance is markedly decreased. The non-protein nitrogen of the blood of Eskimos is similar to that of other races. The results indicate no retention of nitrogenous products in the blood from the habitual high protein diets. Eskimos show a remarkable power to oxidize fats completely, as evidenced by the small amount of acetone bodies excreted in the urine in fasting. The basal metabolism of Eskimos is considerably higher than that of persons living in temperate zones. During fasting the respiratory quotient falls to a level which may be interpreted as indicating a conversion of fat into carbohydrate.

AUTHOR'S SUMMARY.

THE EFFECT OF SCURVY-PRODUCING DIETS AND TYRAMINE ON THE BLOOD OF GUINEA-PIGS. M. T. HANKE and K. K. KOESSLER, J. Biol. Chem. 80:499, 1928.

Tyramine injected subcutaneously into guinea-pigs does not produce nor lead to anemia in well fed guinea-pigs or in animals that are fed deficient diets. There is no evidence, in these experiments, that, in guinea-pigs, a diet deficient in vitamin A is conducive to anemia nor to the production of abnormal erythrocytes. A diet consisting exclusively of autoclaved soy beans and minerals rapidly leads to scurvy symptoms and death. In such animals an abnormal red blood picture is invariably obtained. There is present a marked polychromatophilia, anisocytosis, and poikilocytosis. The smear may contain a high percentage of nucleated red cells. Reticulocytes may be present in quantities up to 25 per cent. The abnormal red blood picture may, occasionally, be associated with an anemia.

AUTHORS' SUMMARY.

BLOOD SUGAR AND RESPIRATORY METABOLISM TIME CURVES OF NORMAL INDIVIDUALS, FOLLOWING SIMULTANEOUSLY ADMINISTERED GLUCOSE AND INSULIN. I. M. RABINOWITCH and E. V. BAZIN, J. Biol. Chem. 80:723, 1928.

The simultaneous administration of insulin and carbohydrate to normal (non-diabetic) persons does not result in an increase in the rate of oxygen consumption, carbon dioxide production or heat production. The normal rates are, on the contrary, significantly depressed, indicating that "insulin not only does not enhance oxidation of sugar in the normal individual, but in some as yet unexplained way interferes with the normal mechanism."

ARTHUR LOCKE.

EXPERIMENTAL EXTRACORPOREAL THROMBOSIS. WALTER R. JOHNSON, TAKUJI SHIONOYA and LEONARD G. ROWNTREE, *J. Exper. Med.* **48**:871, 1928.

The processes of blood coagulation and of thrombosis in the extracorporeal loop are definitely delayed in experimental obstructive jaundice and in animals that have received intravenous injections of bile salts. No attempt is made to explain the changes found in jaundice on the basis of the increased levels of bile acids in the blood although these experiments would indicate that such a possibility has not been ruled out.

AUTHORS' SUMMARY.

BLACKTONGUE PREVENTIVE IN YEAST. JOSEPH GOLDBERGER, G. A. WHEELER, R. D. LILLIE and L. M. ROGERS, *Pub. Health Rep.* **43**:657, 1928.

The blacktongue-producing potency of a basic experimental diet and of three modifications was tested 33 times in 31 dogs with the production of 33 separate attacks of blacktongue. Only one of these attacks developed at the end of a period longer than sixty-one days.

Experimental blacktongue is due to a dietary deficiency which is capable of being corrected by some substance in yeast.

This blacktongue preventive in yeast is inactivated or destroyed by heat sufficient to char the yeast; retains its preventive potency in large measure, if not entirely, after heating in the steam autoclave at a pressure of 15 pounds (6.8 Kg.) for seven and one-half hours; and is adsorbed from an acidulated aqueous extract of either dried yeast or of yeast first autoclaved at a pressure of 15 (6.8 Kg.) pounds for two and one-half hours by English fuller's earth. It cannot be identified with any of the older well recognized dietary essentials, but is believed to be identical with the thermostable substance of Smith and Hendrick.

The blacktongue preventive and the pellagra preventive are both present in yeast. Taken in conjunction with certain other evidence pointing to the fundamental identity of blacktongue and pellagra, this association strengthens the probability that the blacktongue preventive and the pellagra preventive, or vitamin P-P, are identical.

AUTHORS' SUMMARY.

ORGANOTAXIS. G. D. BELONOVSKY and A. A. MILLER, *Ann. de l'Inst. Pasteur* **42**:712, 1928.

Organ emulsions were prepared from ether killed mice, rabbits and guinea-pigs by aseptic removal, washing, grinding with sand and suspension in saline. These were mixed with iron salts, dyes or sodium salicylate and incubated for twelve hours in an oven. The doses that were lethal to mice were determined in chemical studies of the distribution of the foregoing substances. The distribution was definitely influenced by the injection of the organ emulsion with a chemical substance as compared with the injection of the chemical substance alone. Trypan blue emulsified with rat cancerous tumor was also used on cancerous rats. The authors conclude: "The injection of animals with colloidal dyes and with some chemical substances mixed with emulsions of different organs produces an elective concentration of the chemical introduced in the organ an emulsion of which was used; one can assume a double mechanism, positive chemotaxis of the apparent cells (organotaxis), and intensified absorption of the materials by the cells of the organ finding itself in a state of irritation due to the action of specific cytotoxins." Color plates are included.

M. S. MARSHALL.

ANEMIA OF THE TONGUE: AN IMPORTANT EARLY SYMPTOM OF ARTERIAL AIR EMBOLISM. G. LIEBERMEISTER, *Klin. Wchnschr.* **8**:21, 1929.

Air embolism of the tongue with resultant segmental or complete anemia is an early manifestation of arterial air embolism and generally precedes the more severe manifestations. When observed during the collapse of a lung by gas it is an important symptom.

EDWIN F. HIRSCH.

REGULATION OF BLOOD SUGAR, FAT AND CARBOHYDRATE METABOLISM. F. DEPISCH and R. HASENÖHRL, *Klin. Wchnschr.* 9:202, 1929.

The administration of fat (50 Gm.) has no effect on the blood sugar curve in normal persons. Simultaneous estimations of the capillary and venous blood disclose no differences from which may be concluded that a diet of fat does not cause a secretion of insulin. In the patient with diabetes, the blood sugar curve after a diet of fat is parallel with the hunger curve, and there is no difference between the capillary and venous blood. Injection of epinephrine causes in the normal subject, three hours after a diet of fat, a faster and higher increase of blood sugar than the experiment on hunger control which reveals an abnormal mobilization of liver glycogen by the fat. A diet of fat diminishes the effect of the exogenous administered as well as the endogenous insulin.

AUTHORS' SUMMARY.

THE PATHOLOGIC PHYSIOLOGY OF THE ENDEMIC GOITER. F. DE QUERVAIN, *Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927.* Edited by Hans Huber, Bern, 1928.

The pathologic physiology of endemic goiter should cover all the morbid manifestations of the goiter noxa in the human body, and not only the gross anatomic changes in the thyroid gland to which the name of goiter is given. The goiter noxa can affect the structure and functions of the organism: (a) indirectly, by injuring the genital glands of parents and by functional inefficiency of the maternal organism; (b) by direct action on the tissues of the body; (c) by injuring the thyroid gland either directly or by functional overwork, and (d) by injuring the other endocrine glands, either directly or as a result of injury to the thyroid gland.

Taking clinical and experimental facts as a basis, endemic goiters may be divided into: (a) euthyroid goiters with intermediate stages toward hyperthyroidism and hypothyroidism; (b) hyperthyroid goiters, "struma basedowificata," in various forms, principally that produced by iodine, and (c) hypothyroid forms including endemic cretinism in one of its clinical aspects.

In endemic cretinism the following types are to be distinguished: (a) cretinism without goiter, always accompanied by atrophy of the gland and impairment of growth, and (b) cretinism with goiter, with various degrees of atrophy of the rest of thyroid tissue and varying functional capacity of the goitrous tissue. The striking disparity in the clinical manifestations of the two groups of cretinism may be accounted for by: (a) hereditary factors; (b) variations in the earliness and rapidity of onset of injury to the thyroid gland; (c) qualitative modifications of the secretion (relative and, perhaps, absolute dysthyroidism); (d) primary or secondary involvement of other endocrine glands, and (e) direct, extrathyroidal action of the goitrous noxa.

The iodine content of the blood is maintained at a constant level within the limits of seasonal variations. The iodine content is determined by the degree of functional activity of the thyroid gland. For a given intake of iodine, it is at its highest in Graves' disease, is approximately normal in the case of euthyroid goiter and is abnormally low in cretinism with or without goiter.

AUTHOR'S SUMMARY.

ETIOLOGY AND EPIDEMIOLOGY OF ENDEMIC GOITER. R. MCCARRISON, *Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927.* Edited by Hans Huber, Bern, 1928.

Three types of simple goiter are described: The first is the classic type occurring in mountainous regions and variously named parenchymatous goiter, adenoparenchymatous goiter, simple hyperplastic goiter and chronic hypertrophic goiter; the second is the diffuse colloid goiter, and the third is called the lymph-adenoid goiter. The goiter-producing influences known are deficiencies and excesses in food, polluted water supplies, gastro-intestinal infection and insanitary conditions

of life. It is impossible to assert that all cases of goiter originate from the same cause. We now know that goiter is a generic term which includes a variety of diseases of diverse etiology. Future research may further subdivide the simple goiters, clinically, pathologically and etiologically. But meanwhile large numbers of them may be prevented by attention to the fundamental principles of nutrition and of personal and social hygiene.

AUTHOR'S SUMMARY.

ETIOLOGY AND EPIDEMIOLOGY OF ENDEMIC GOITER. B. GALLI-VALERIO, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927. Edited by Hans Huber, Bern, 1928.

The causation of endemic goiter is not yet fully understood.

Of the numerous theories that which establishes drinking water as the cause of goiter is at once the oldest and the best supported by fact and experiment, as shown by the following observations: (a) the detection of contamination of the drinking water in all endemic districts; (b) the abatement and disappearance of the endemic under improved conditions of the supply of drinking water, and (c) the appearance of goiter in animals that have been watered from sources in endemic districts or with artificially contaminated water.

The noxa of goiter in drinking water is either a specific substance or a specific germ or group of germs, especially of the intestinal flora, which produce toxic substances that act on the thyroid gland. As a consequence, disinfection of the bowel is beneficial and a regimen favoring constipation is the reverse.

The theory that establishes drinking water as a cause does not exclude the possibility of other vehicles for spreading the endemic. In like fashion, cholera, enteric fever and dysentery, in all of which the drinking water is usually at fault, can equally be conveyed by milk, vegetables, direct infection, etc.

Apart from water supply inbreeding is a predisposing factor in cretinism and deafmutism.

The theory of the causation of goiter by deficiency of iodine cannot be accepted: (a) because even where iodine is present in excess (sea-coast and sea) goiter may develop, and (b) because deficiency of iodine causes atrophy, not hypertrophy, of the thyroid gland.

Iodine is merely, in some way, an antidote to goiter, as is quinine to malaria. The theory that goiter is caused by drinking water has much to recommend it from the side of prophylaxis as it leads to an improvement of the water supply.

AUTHOR'S SUMMARY.

THE GEOGRAPHICAL DISTRIBUTION OF ENDEMIC GOITER. E. BIRCHER, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927. Edited by Hans Huber, Bern, 1928.

Endemic goiter is part of a complex pathologic manifestation characterized by a distinct geographic distribution. In the countries where it prevails it can present temporary variations of different intensity, as increase or diminution. In the countries where endemic goiter prevails, the goiter varies in its character. Endemic goiters of different countries cannot be compared with each other, as the difference is both quantitative and qualitative. The histologic structure is also of pronounced variety. The etiologic factor of goiter and the conditions which favor its prevalence are of a varied nature. One cannot admit a uniform etiologic factor.

AUTHOR'S SUMMARY.

THE FORMATION OF BILE. LUDWIG ASCHOFF, Acta path. et microbiol. Scandinav. 5:338, 1928.

This is a lecture in which present knowledge of the formation of bile and its disturbances are discussed. The following scheme is presented:

Hyperfunctional types: Icterus in pernicious anemia, familial icterus and icterus neonatorum.

Retentional type: icterus in dogs deprived of the liver.

Retentional and resorptional type: icterus in starvation.

Hyperfunctional, retentional and resorptional types: Catarrhal icterus, infectious icterus (Weil's disease) and toxic septic icterus.

Resorptional type: mechanical icterus.

Aschoff uses the word dyscholia to signify disturbances in the formation and elimination of bile-forming substances.

A long list of references is given.

Pathologic Anatomy

COMMUNICATING HYDROCEPHALUS. JOSEPH H. GLOBUS, *Am. J. Dis. Child.* **36**: 680, 1928.

In two of the five cases presented in this report there was almost complete obliteration of the subarachnoid channels. Because of the embryonal structure of the pia mater and the absence of evidence of inflammatory changes, it was assumed that the defect was on a developmental basis.

The third case differed from the first two in that the hydrocephalus was less marked and of slower development. This picture results from the fact that a small number of the channels had opened.

The fourth and fifth cases illustrate respectively the type of hydrocephalus due to obliteration of the subarachnoid channels by infection, and the type resulting from organization of traumatic hemorrhagic exudate.

Dandy and Weed, although disagreeing as to the mechanism, are both of the opinion that a patent subarachnoid space is essential for the normal distribution of cerebrospinal fluid. When there is an obstruction of the channels without blockage of the flow of spinal fluid between the ventricular cavities, the result is communicating hydrocephalus.

The dye test helps to differentiate the obstructive type from the communicating type.

H. E. LANDT.

BLOOD IN THE STOOLS OF THE NEW-BORN. BASNET E. BONAR, *Am. J. Dis. Child.* **36**:725, 1928.

The benzidine test for occult blood was found positive in 29.38 per cent of 1,518 stools of 109 new-born. Occult blood is found too frequently in the stools of the new-born to ascribe its cause to the usual sources. Neither should it be considered physiologic. Certain observations seem to warrant the assumption that the bleeding is due to an intense hyperemia set up in the upper portion of the small intestine by products of digestion, by the primary bacterial invasion, or by both. More attention should be given the so-called initial diarrhea of the new-born which appears to be another manifestation of the irritability of the bowel which occurs in early days of life.

AUTHOR'S SUMMARY.

SICKLE CELL ANEMIA. MARTHA WOLLSTEIN and KATHERINE V. KREIDEL, *Am. J. Dis. Child.* **36**:998, 1928.

In New York, sickle cell anemia is as common as it is in cities of the South and West. In a series of fifteen negro children whose blood showed sickle cells, twelve were in the active phase and three were in the latest phase. In three of the active cases, the patients died of the anemia without other anatomic cause for death. All showed fatty degeneration of the myocardium and liver, distention of the sinuses of the spleen with sickle cells, phagocytosis of the sickle cells by Kupffer cells in the liver and iron pigment in the spleen, liver and kidneys. In two latent cases the patients died of tuberculosis, and in one the patient died of pneumococcus meningitis. Syphilis was present in one child of the series.

AUTHORS' SUMMARY.

HEART-BLOCK DUE TO PRIMARY LYMPHANGIO-ENDOTHELIOMA OF ATRIO-
VENTRICULAR NODE. PUTNAM C. LLOYD, Bull. Johns Hopkins Hosp. 44:
149, 1929.

A case is described in which a lymphangio-endothelioma had invaded the atrio-ventricular node and the bundle of His, and caused a partial heart-block, terminating in sudden death.

AUTHOR'S SUMMARY.

THE PHAGOCYTOSIS OF MELANIN BY THE RETICULO-ENDOTHELIAL CELLS IN A
CASE OF MELANOBLASTOMA. C. V. WELLER, Warthin Ann., 1927, pp. 547-557.

The occurrence of melanin in the reticulo-endothelial cells situated near, but apart from, an area of melanoblastoma is common. The presence of melanin in organs and tissues distant from those in which the melanoblastomatous neoplasms occurred has been an infrequent observation; Weller describes such a case. The primary growth was a melanoblastoma of the left eye, which had been enucleated two years before death occurred. The liver showed multiple nodular deeply pigmented metastases. Multiple pigmented metastases were likewise found in the cranium, ribs, sternum and vertebrae. The suprapancreatic, mesenteric, retroperitoneal, bronchial and mediastinal lymph nodes were larger than normal and of a brownish-black color. Small pigmented areas were seen in the suprarenals and in the renal cortex; these had the gross appearance of metastases.

Microscopic studies of the non-neoplastic areas of the liver revealed that melanin was found in granules and dense clumps in the reticulo-endothelial cells. Many of the reticulo-endothelial cells of the leptomeninges contained melanin. In the spleen, even though there were no neoplasm cells, there was well marked melanin deposition in the reticulo-endothelial cells. The lymph nodes revealed an abundance of pigment confined to the reticulo-endothelial cells, entirely like that found in the neoplastic areas of the liver; the lymph nodes showed no metastases of neoplasm cells. Similar phagocytosis of melanin in the absence of neoplasm cells was observed in the suprarenals, gastro-intestinal tract, bone marrow and kidneys. Careful microchemical studies were carried out in order to establish the identity of the pigment.

Weller considers that the distribution and morphology of this pigment can best be explained by the assumption that groups of reticulo-endothelial cells exercise an active selective phagocytosis of the precursors of melanin and that through enzymatic or other intracellular activity melanin is elaborated within the cells. Weller suggests that this mechanism may explain the presence of chromatophores in the meninges of normal persons, particularly of the negro race.

WALTER M. SIMPSON.

CRANIOSYNOSTOSIS (OXYCEPHALY AND RELATED DISORDERS). H. K. FABER,
Warthin Ann., 1927, pp. 585-600.

Faber includes as varieties under the generic term "craniosynostosis" such cranial deformities as oxycephaly (steep-skull), turriccephaly (tower-skull), scaphocephaly, trigonocephaly and phagioccephaly. All have their origin in pathologic synostosis of two or more bones of the calvarium, and are associated in a certain proportion of cases with deformities resulting from synostosis or fusion of adjoining bones in other parts of the body. The anterior and superior portions of the skull (coronal and sagittal sutures) are most frequently involved.

The malformations are conditioned by two factors; first, interference with normal expansion and, second, compensatory overexpansion of unsynostosed regions to accommodate the growing brain. The mechanisms of the development of these deformities are discussed in detail.

The instances of craniosynostotic deformities in more than one generation of a given family are exceptional. More common are examples of their appearance in more than one member of the same generation.

The distinguishing feature in the diagnosis is that the cranial cavity, while deformed, is of normal volume. Visual defects are common and greatly influence the prognosis.

WALTER M. SIMPSON.

DIVISION OF CELLS UNDER VARYING TENSIONS OF CARBON DIOXIDE. J. C. MOTTRAM, *Brit. J. Exper. Path.* 9:240, 1928.

Mitoses of normal cells cultivated in vitro occur most abundantly at a carbon dioxide tension approximating that of normal tissues. Under high tensions, abnormal mitoses occur in which there is an irregular migration of the chromatin to the centrosomes.

PEARL ZEEK.

VERTEBRAL HYDATID CYST. F. DÉVÉ, *Ann. d'anat. path.* 5:84, 1928.

Dévé affirms that there is no such thing as hydatid cyst of the vertebrae. Experimental and clinical observations led him to the conclusion that the parasite invades this structure in the form of a diffuse osseous microvesicular infiltration. He could never find a regular capsule surrounding the univesicular or multivesicular echinococcus parasite. He therefore recommends to replace the expression of older observers "hydatid cyst" by the term "vertebral echinococcosis." He further states that the disease begins as a miliary multilocular lesion and the spongy bony tissue appears to be infiltrated by multiple minute vesicles, which advance by continuity without causing any osteomyelotic reaction. Likewise, the presence of echinococcus in the spinal canal is in all probability of exogenous osseous origin.

B. M. FRIED.

NODULAR PERIARTERITIS. R. DEBRÉ, R. LEROUX, P. GAUTHIER-VILLARS and LELONG, *Ann. d'anat. path.* 5:757, 1928.

With the naked eye the lesions are seen as miliary nodules distributed along blood vessels. With the microscope the entire blood vessel appears to be involved. The intima is thickened and edematous; in the media both elastic membranes show dissociation and often complete destruction. The adventitia is infiltrated with polymorphonuclear leukocytes which also surround the vessel; the vascular lumen is narrowed, irregular and occasionally completely obliterated. However, the microscopic characteristics of the lesion depend on the stage or severity of the disease. The vascular lesions are accompanied by degeneration of the peripheral nerves, by hemorrhages in the brain and in the gastro-intestinal tract, and also by marked lesions in the kidneys. In order of frequency the coronaries, the renal and the hepatic vessels are the more commonly involved; then go the mesenteric, the gastric, intestinal, splenic, pancreatic, etc.

The clinical picture is extremely variable, pointing to a polyneuritis, cardiac insufficiency or to a disease of the peritoneum. The duration of the disease varies from a few days to two years. It is not necessarily fatal. The majority of authors believe it to be caused by a micro-organism. It has been found also in some animals as the pig, the calf and the dog. The authors report a personal observation, discuss the cases from the literature and also give a good bibliography on the subject.

B. M. FRIED.

A MIXED EPITHELIOMA OF THE KIDNEY. P. MASSON and C. SIMARD, *Ann. d'anat. path.* 5:825, 1928.

The case reported by Masson and Simard concerned an epithelioma of the kidney which had two different structures; in one place it resembled tumors originating in the renal pelvis, in the other it looked like carcinoma of the convoluted tubules. Both varieties spread toward and invaded the renal parenchyma. The authors discuss the possibility of this tumor being a primary "double" cancer of the kidney. They are inclined to the belief that both varieties of the neoplasm

originated in the renal excreting epithelium. The complexity of its structure is in all probability being due to the evolutionary potentialities of the excreting epithelium which is capable of giving rise to tumors resembling those of the convoluted tubules.

B. M. FRIED.

NODULAR SCLEROSIS ACCOMPANIED BY A PULMONARY PANARTERITIS IN SYPHILIS OF THE LUNG. H. DARRÉ and G. ALBOT, *Ann. d'anat. path.* **5**:861, 1928.

Syphilis of the lung may take different aspects: a peribronchial sclerosis or a nodular disseminated fibrosis confined to the perilobular, perialveolar and inter-alveolar tissues associated with a pulmonary panarteritis. There may be no lesions of the bronchi. In instances in which the disease is predominantly confined to the arteries, the pathologic modification resembles those found in the liver, kidneys and other organs. From a clinical standpoint the symptoms are those of cardiac insufficiency.

B. M. FRIED.

MUCOUS SECRETION AND MUCOUS CYSTS IN ADENOCARCINOMA OF THE CORPUS UTERI. ISBRUCH, *Arch. Gynäk.* **135**:102, 1928.

By differentiation of the malignant cells, two types of cysts are formed, one containing true mucus taking a mucicarmine stain, and the other containing a homogeneous substance representing a different type of secretion. Isbruch noted that the epithelial cells of the mucous cysts were somewhat higher than those of the other cysts.

A. J. KOBAK.

MORPHOLOGY OF WHITE BLOOD CELLS IN ENTERAL SENSITIZATION AND ANAPHYLAXIS. R. GAWRILOW, *Virchows Arch. f. path. Anat.* **265**:583, 1927.

No definite change in the blood picture was found in rabbits during feedings of egg white or yolk. Relatively often a moderate leukocytosis occurred, with increase in lymphocytes, and without characteristic changes in the other cells. During the following latent period, the white cells were normal or remained slightly increased. Intravenous injections of the same protein were made from fourteen to eighteen days later. In the case of egg white, leukopenia with reduction in eosinophils and increase in lymphocytes occurred at first, and was sometimes followed by leukocytosis with reduced lymphocytes. With egg yolk, there was also a transitory leukopenia, with subsequent leukocytosis, but the reaction to this protein was less marked.

B. R. LOVETT.

THE SECONDARY NODULES IN LYMPH NODES. W. ROTTER, *Virchows Arch. f. path. Anat.* **265**:596, 1927.

Rotter distinguishes five types of nodules in lymph nodes: solid or resting, epithelioid, reticular, lymphoplastic and necrotic. If these bodies are to be regarded as centers for immunity reactions instead of as germinal centers, their derivation should be from the reticulo-endothelial system. The epithelioid nodules apparently develop from the cells of the blood vessel walls. The nodules then take on a reticular structure, in which the large, free cells, lymphoblasts, develop, probably from the fixed tissue cells. The author believes that the small lymphocytes do not differentiate farther, but that the damaged ones are destroyed in the central space of the nodules, where remains of their nuclei may be found. He formulates the theory that the secondary nodules arise as a reaction principally to hematogenous irritation, the speed and form of the reaction being largely determined by the degree of sensitization of the organism to the irritant. Lymphogenous irritation may also lead to the formation of these centers. He therefore regards them as reaction centers of immunologic significance, but agrees that during retrogression of the lymphoplastic nodules to the resting stage, they act as germinal centers for the new formation of lymphocytes.

B. R. LOVETT.

AMYLOID IN A TUMOR OF THE CERVICAL LYMPH NODES. K. v. GUSNAR, Virchows Arch. f. path. Anat. **265**:617, 1927.

A local deposit of a homogenous substance was found in a metastatic carcinoma of the cervical lymph nodes. This substance gave the color reactions characteristic for amyloid through most of its extent. Similar masses were also found in the newly developed cells, evidently a hyaline precursor of the amyloid. A sharp distinction between amyloid and hyaline substance cannot always be established.

ADENOMA OF THE FALLOPIAN TUBE. A. PRIESEL, Virchows Arch. f. path. Anat. **265**:630, 1927.

In an operation on a woman, aged 30, cherry-sized nodules resembling adenomyomas were found on the uterine portions of both tubes. Histologic examination of one of them showed a fibro-epithelial new-growth, with glandular structures surrounded by cellular tissue. Most remarkable was the presence of numberless islands of pavement epithelium mixed with the cylindrical epithelium of the glands. Pavement epithelium has not, to the author's knowledge, been described in the tubes before, although it is sometimes found in the uterus. Priesel regards these nodules as due to a developmental anomaly, and not to an inflammatory process, partly on account of the presence of the two types of epithelium. The tumors were apparently benign.

B. R. LOVETT.

CONGENITAL LIPOMA OF THE FEMORAL VEIN. J. GANGLER, Virchows Arch. f. path. Anat. **265**:643, 1927.

A lipoma the size of an orange was removed from the femoral vein of a girl, 18 months of age. The vein ran through a groove in the mass, which was surrounded by a fibrous capsule everywhere except where there was contact with the vein. The point of origin appeared to be the adventitia of the vein. Since this tissue does not normally contain fat cells, the development of a lipoma from it is evidence for the theory of embryonic displacement of tissue rests as a cause of tumor development.

B. R. LOVETT.

HISTOLOGY OF NEURINOMAS. F. NESTMANN, Virchows Arch. f. path. Anat. **265**:646, 1927.

Verocay distinguished neurinomas from neuromas by the arrangement of nuclei in rows or palisades, but the specificity of this structure for neurinomas has been questioned, since it is also found in other, usually mesodermal, tissues. The author examined ten neurinomas. He regards mechanical factors as the cause of the palisade arrangement of nuclei in tissues with fibrillar structure. In smooth muscle, contraction and hyalinization or other regressive changes are responsible; in neurinomas the abundant growth of fibrils pushes the nuclei into this position. The palisades found in these tumors can, however, be distinguished from others by the characteristic ground substance, consisting of delicate parallel fibrils. Two types of tumors have been described, which, the author finds, represent different lines of development rather than successive stages.

B. R. LOVETT.

BRAIN CYSTS. W. SCHLEY, Virchows Arch. f. path. Anat. **265**:665, 1927.

Schley described six cases of cysts of the brain, in all of which a tumor, usually a glioma or angioma, was found. He agrees with Lindau's view, that these cysts arise by transudation of fluid from a preexisting tumor, due to disturbances in circulation. The tumor tissue may be discoverable only with the microscope. Not only angiomas and gliomas, as described by Lindau, may lead to cyst formation, but other types as well, in one instance a metastatic growth from a bronchial carcinoma. The vascularity of the tumor and disturbances in

the local circulation are the determining factors. While cysts have usually been found in the cerebellum, they may arise in the cerebrum or pons in the same manner, as described in two of the author's cases.

B. R. LOVETT.

PATHOLOGY OF THE CEREBRAL VESSELS: I. CEREBRAL HEMORRHAGE. E. POLLAK and P. REZEK, Virchows Arch. f. path. Anat. 265:683, 1927.

Four instances of extensive hemorrhages of the brain were investigated pathologically, with reference to the theory of Westphal and Baer. According to this, a spasm of the vessels leads to anemia and autolysis of the wall, followed by increased permeability and bleeding; an acute rather than a chronic process. The authors found marked differences in the condition of the vessels at varying distances from the hemorrhagic zone. In this zone itself, the walls were entirely necrotic, and no cellular reaction was visible. At the border, the beginning of cellular reaction could be seen, but edema with splitting of the vessel wall was the chief change. Still farther away, partial necrosis was found, involving only a single coat, usually the media or elastic tissue, or only a short section of the vessel. Accumulations of cells surrounded the necrotic foci.

While it was not possible to draw conclusions as to the mechanism of cerebral hemorrhage from these morphologic changes, the authors found them incompatible with the theory of Westphal and Baer. The picture was that of a chronic process of long duration, leading to a partial necrosis of the blood vessel walls. Sometimes marked necrosis of the media was found without any surrounding hemorrhage. Of the older theories, rupture of a vessel wall or the formation of small aneurysms as causes of bleeding could not be substantiated either. The authors regard vasomotor disturbances as an important factor, with the partial necrosis of the wall impeding its response to changes in a blood pressure already high. Consequent splitting of the layers permits the passage of blood through the wall.

B. R. LOVETT.

LYMPHATIC REACTION IN THE WALL OF THE APPENDIX. K. NISHIKAWA, Virchows Arch. f. path. Anat. 265:735, 1927.

Nishikawa examined serial sections of 111 appendixes for the presence of lymphatic tissue in the regions where this is not found normally, namely, in the muscularis, subserosa, serosa and the mesentery. In sixty-one cases he found lymphatic tissue in successive stages of development, from simple collections of lymphocytes to fully mature nodes, with capsule, germinal centers and sinuses. This reaction was shown to be independent of age and of variations in the lymphoid tissue of the mucosa. It was associated with chronic and with recurring inflammations, and was present in the stage of healing, but never during acute inflammations. It appeared to be not a part of the inflammatory process itself, but a secondary process, continuing independently of the inflammation.

B. R. LOVETT.

RENAL CHANGES IN NUTRITIONAL DISTURBANCES OF INFANTS. H. STROHE, Virchows Arch. f. path. Anat. 265:765, 1927.

Histologic examination of the kidneys of fifty-six infants dying with nutritional disturbances revealed in the cortex thickening of the capsular epithelium, exudation into the capsular space, cloudy swelling, fatty changes and cellular infiltrations, especially around the blood vessels. The changes in the medulla were more extensive. All the changes of circulatory disturbance were observed, from hyperemia, with and without degenerative changes in the surrounding parenchyma, stasis with necrosis of the tubular epithelium, serous or cellular exudation into the interstitial tissue, to degenerative changes (hyalinization, etc.), and cellular proliferation. Exudation of red cells into the interstitial tissue was frequent, and

consequent pigmentation in older cases. Hemorrhagic infarction, and less frequently purulent interstitial nephritis, form the end-stage which may follow the foregoing changes. Different stages were found at times in the same kidney, and often the two kidneys presented different appearances. The presence of bacteria in the blood bore no relation to the renal changes. In most fatal diseases of infants such changes are to be found, and are probably related to the disturbance in nutrition. When extensive and productive of clinical symptoms, the condition may be referred to as nephritis of infancy.

B. R. LOVETT.

ANGIOSPASM AS A CAUSE OF RENAL INFARCTS. K. NEUBÜRGER, *Virchows Arch. f. path. Anat.* **265**:789, 1927.

The author made a study of functional disturbances of the circulation as a cause of infarcts in the kidney. Several ischemic infarcts were examined, in which no thrombosis and no disease of or injury to the vessel walls was present, and the conclusion reached that spasm of the renal artery, following operative trauma in the vicinity, was the most probable cause. An instance of gangrene of the leg following an injection of hexatone in an infant with whooping cough was also attributed to traumatic angiospasm.

B. R. LOVETT.

MORPHOLOGY AND MICROCHEMISTRY OF THE ANIMAL CELL: DEMONSTRATION OF THE CELL MEMBRANE. M. GUTSTEIN, *Virchows Arch. f. path. Anat.* **265**:805, 1927.

Several staining methods are described for demonstrating the membrane system of the cell, including the membrane of the cell itself, of the nucleus, and of the nucleolus. Either an acid (tannin) or a basic (alum) mordant is used, followed by a stain of the opposite reaction. Since the three membranes, as well as certain protoplasmic granules, are all stained by these methods, there must be some similarity in their chemical structure. That the granules are not artefacts could be shown by their presence also in supravital stained preparations. Both acid and basic substances are present in the cell membranes. Experiments in solubility in different fluids give the following results: The acid body is a lipid, bound to the basic ground substance. The acid mordant combines with the latter, the basic mordant with the acid lipid. This lipid resembles the phosphatids in its staining reactions. The same methods can be used for staining bacteria.

B. R. LOVETT.

RELATIONS BETWEEN OXYDASES, VITAL STAINING, POSTMORTEM STAINING, AND MORPHOLOGY OF THE CELL. W. LOELE, *Virchows Arch. f. path. Anat.* **265**:827, 1927.

Loele finds that oxydases and peroxydases, which can be demonstrated by different phenolase reactions, are not uniform bodies, but mixtures of substances. They may occur independently of each other. Oxydases are not necessary for vital staining, but oxydase-containing substances lend themselves easily to staining by vital methods. The process need not cause cell injury, especially if an acid stain is used. By means of the secondary naphthol reaction, different types of cell nucleoli can be distinguished: a single round body, several round ones, irregular and variable bodies and nuclei without nucleoli. The alterations of the nucleoli of a single cell type during a disease process are described, and further morphologic changes in nucleoli and chromosomes.

B. R. LOVETT.

ALEUKEMIC MYELOSIS WITH OSTEOSCLEROSIS OF THE SKELETON. A. JORES, *Virchows Arch. f. path. Anat.* **265**:845, 1927.

Jores described a case of hematopoietic disease, corresponding to aleukemic myeloid leukemia, of twelve years' duration, accompanied by sclerosis of the entire

bony system. In the much narrowed marrow cavities, there was both fibrous and actively functioning marrow. He regarded the disease of the marrow as primary, with the bony changes secondary to it.

B. R. LOVETT.

PATHOLOGIC PHYSIOLOGY OF GOITER. B. BREITNER, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927. Edited by Hans Huber, Bern, 1928.

A comparison of the iodine content of the blood of the arteries and veins of the thyroid gland and the veins of the arm with that of the goiter appears to prove the existence of a thyroïdal secretion escaping into the blood current. Results of experiments made by infusing specimens of blood from these different sources into the larvae of salamanders, point in the same direction. The action of iodine on persons with goiter corresponds to that which has been observed by experiments on animals. Subjects who are to be treated with iodine should therefore be carefully selected.

Clinical and experimental observations agree as to the morphologico-functional types of goiter conditioned by "hyporrhoe" and "hyperrhoe." The author's point of view is based (1) on the appreciation of the two principal functions of the thyroid gland, namely, the production and the elimination of secretion and on the functional adaptation of the gland and (2) on the discrimination between the activity and the output of this organ. Bearing in mind the rôle of the sympathetic nervous system in the secretory process of the thyroid gland, this point of view enables him to establish a complete theoretic schema of the functional diseases of the thyroid gland.

ETIOLOGY AND EPIDEMIOLOGY OF THE ENDEMIC GOITER IN FRANCE. L. BÉRARD and C. DUNET, Transactions of the International Conference on Goiter, Bern, Switzerland, Aug. 24-26, 1927. Edited by Hans Huber, Bern, 1928.

In France, thirty-seven departments are subject in varying degrees to endemic goiter; in the other forty-nine departments goiter is only exceptionally encountered. The geographical distribution of goiter in France has not changed during the past thirty years.

Altitude and climate play only a subsidiary part in the genesis of goiter. This is proved by the fact that goiter has decreased in intensity though its geographical distribution has remained the same. No systematic preventive treatment with iodine has come to light. The cause of the decrease is assumed to be: (a) the improvement of the drinking water, (b) the increase in the consumption of wine, (c) emigration (temporary or permanent) from the goitrous districts, (d) a decrease in the number of marriages between blood relations, and (e) the improvement in the general conditions of living (personal and general hygiene and improvement of conditions in the home and of nourishment).

Although there are several causes of endemic goiter, drinking water is the most prominent. There are beyond all doubt certain kinds of water which produce goiter. The action of goiter-producing water is to be explained by its interference with iodine metabolism, causing relative or complete insufficiency of iodine. All factors therefore which increase the need of the system for iodine favor the appearance of goiter (puberty, pregnancy, lactation and the climatic period). Goiter is regarded not as a disease strictly confined to the thyroid gland, but as a general disturbance of nutrition.

The type of endemic goiter that is usually found in France is struma nodosa parenchymatosa or cystica. Diffuse hyperplasia of the thyroid gland is only rarely observed. Toxic goiter is rare. New growths of the thyroid gland are also rare. In carcinoma of the thyroid gland, 85 to 90 per cent of the cases occur as a result of an already existing goiter.

AUTHORS' SUMMARY.

Microbiology and Parasitology

EPIDEMIOLOGIC AND BACTERIOLOGIC INVESTIGATION OF THE SLOANE MATERNITY HOSPITAL EPIDEMIC OF HEMOLYTIC STREPTOCOCCUS PUERPERAL FEVER IN 1927. F. L. MELENEY, ZUNG DAU ZAU, H. ZAYTOZEFF and H. D. HARVEY, *Am. J. Obst. & Gynec.* **16**:180, 1928.

During the period from Jan. 18 to Feb. 18, 1927, an epidemic of puerperal fever raged in the Sloane Maternity Hospital; approximately 15 per cent of all pregnant patients developed the disease, with an approximate mortality rate of 33 per cent. The lochial discharges of all except one of the mothers affected revealed *Streptococcus hemolyticus*. Five of the strains were proved antigenically identical by cross agglutination and by crossed absorption of the agglutinin tests. Nineteen other strains were closely related to if not identical with the aforementioned strains. Some of the nurses and doctors were found to be carriers of these organisms, harboring them in the nose or throat. On serologic study the strains from the nose of one of the nurses was found identical with the puerperal strains. From an axillary abscess of a nurse whose finger was pricked, and from the peritoneal exudate of another nurse with peritonitis, strains were obtained which were like the five identical strains from the patients with puerperal fever. Cultures of the air of the wards and operating rooms, cultures of linen supplies and sterilized supplies yielded no hemolytic streptococci. The peak of fever, indicating the clinical onset, occurred usually on the fourth day. The vagina was considered the portal of entry and the organisms were conveyed to the patient by carriers.

A. J. KOBAK.

THE BACTERIAL CONTENT OF THE UTERUS AT CAESAREAN SECTION. II. J. W. HARRIS and J. H. BROWNE, *Am. J. Obst. & Gynec.* **16**:332, 1928.

Twenty-two among fifty uteri from which cultures were obtained at cesarean section were found to be infected. After six hours of labor the authors found that the amniotic cavity was invariably infected, even though the fetal membranes were intact. The second part of this report describes the bacteria that were recovered. Streptococci in numerous strains, *Staphylococcus albus* and diphtheroids were found most frequently. All the patients but one had a febrile puerperium, but all recovered. Healing of the incision was retarded when it contained any of the bacteria recovered in the amniotic contents.

A. J. KOBAK.

SEPTICEMIA DUE TO A STRAIN OF THE BACILLUS MUCOSUS IN DIABETES MELLITUS. E. H. MASON and W. M. BEATTIE, *Arch. Int. Med.* **42**:331, 1928.

Septicemia from *Bacillus mucosus* has been reported in seventy-eight cases. In the case reported here blood culture gave a capsulated organism considered a variant of the *B. mucosus* group. The infection occurred in a case of food-controlled diabetes and resulted in death in about two weeks.

HAMILTON R. FISHBACK.

BRONCHOMONILIASIS. W. R. GALBREATH and C. WEISS, *Arch. Int. Med.* **42**:500, 1928.

Monilia infection of the lungs may be of a mild, intermediary or severe form. The symptoms in general are: dyspnea, cough, expectoration, with or without blood, and fever. There are frequent remissions and exacerbations. In the severe type the course resembles that of pulmonary tuberculosis and almost invariably ends fatally. Potassium iodide is the specific remedy. Other treatment may be the same as for tuberculosis. Monilia may be recovered from the sputum, or from the lesions at autopsy. A case is reported with a history of pulmonary

symptoms since 1918, the patient now being in a good state of nutrition and continuing his occupation. *Monilia psilosis* (ashfordi) has been repeatedly found in the sputum.

HAMILTON R. FISHBACK.

SYNOVIAL FLUID IN CHRONIC ARTHRITIS. C. E. FORKNER, A. R. SHANDS and M. A. POSTON, Arch. Int. Med. 42:675, 1928.

In a study of sixty-three cases of chronic arthritis, excluding syphilitic and tuberculous infections, positive cultures were obtained in 22 per cent. Cultures from the lymph nodes were positive in 48 per cent of twenty-one cases; in 24 per cent the same type of organism was recovered from joint and lymph nodes. In all cases, the number of white cells was increased, the bacteriologically positive cases showing almost twice as many as the negative cases. The number of polymorphonuclears was increased in the positive group, while the monocytes and lymphocytes predominated in the negative group. Synovial mesothelial cells were not seen constantly.

HAMILTON R. FISHBACK.

SYPHILIS OF THE STOMACH. H. A. SINGER and F. G. DYAS, Arch. Int. Med. 42:718, 1928.

A case is detailed with a primary clinical diagnosis of gastric syphilis. Following roentgen examination and associated observations of ulcer, a partial gastrectomy was performed. Multiple ulcers were found. No classic gumma was present, and *Spirochaeta pallida* could not be demonstrated. Below the ulcers, in which fusospirilla of Vincent were present, the principal lesions were in the thickened submucosa. There were focal granulomatous lesions which were composed chiefly of lymphoid and plasma cells, with a marked perivascular distribution. No case has been found in the literature which meets the demands for a pathologic diagnosis of gastric syphilis, that is, the presence of a classic gumma, or the certain demonstration of *Spirochaeta pallida*.

HAMILTON R. FISHBACK.

A STUDY OF MICROCOCCUS ZYMOGENES. MARTIN FROBISHER, JR., and E. RANKIN DENNY, J. Bact. 16:301, 1928.

The resemblance of the organisms studied as *Micrococcus zymogenes* to *Streptococcus liquefaciens* is such as to suggest that the former are merely varieties of the latter or that the two are identical. *M. zymogenes* should be classed as a streptococcus. The proteolytic enzymes of these organisms resemble histase in their action on cooked meat but differ from this enzyme in their ability to digest coagulated serum, gelatin and casein as well. There appears to be no relation between hemolysin and proteolytic enzyme production by these organisms. The literature reveals nothing to suggest a direct relationship between *M. zymogenes* and any special type of pathologic condition, although organisms called *M. zymogenes* have been more frequently isolated from endocarditis than from any other single disease. Proteolytic streptococci of the type represented by *S. liquefaciens* might be more frequently reported in pathologic bacteriology if more detailed study of the proteolytic activity of streptococcus-like organisms were made as a routine.

AUTHORS' SUMMARY.

SUSCEPTIBILITY OF ESKIMOS TO THE COMMON COLD AND A STUDY OF THEIR NATURAL IMMUNITY TO DIPHTHERIA, SCARLET FEVER AND BACTERIAL FILTRATES. PETER HEINBECKER and EDITH I. M. IRVINE-JONES, J. Immunol. 15:395, 1928.

Eskimos are very susceptible to infections of the upper respiratory tract on contact with the outside world. Ordinary bacterial infections rarely occur. Diphtheria and scarlet fever are unknown clinically. In a group of about fifty subjects all gave negative reactions to the Dick test and also, in the case of the adults, to the Schick test. Children up to the age of 12 years invariably gave positive reactions to the Schick test. Three serums were found to contain antitoxin both

for diphtheria and for scarlet fever. It is therefore concluded that the immunity to the disease and the negative reaction to the skin tests depend on the presence of antitoxin. This is interpreted as being due to a natural hereditary immunity dependent on some nonspecific antitoxic mechanism. Skin reactions with filtrates of streptococci isolated from cases of rheumatic fever were mildly positive in a small percentage of cases. Neutralizing antitoxin was demonstrated in all three serums but it was not invariably present for all three toxins. The Eskimos showed a high percentage of positive reactions when tested with a *Staphylococcus aureus* filtrate.

AUTHORS' SUMMARY.

INFECTION OF A LABORATORY WORKER WITH *BACILLUS INFLUENZAE*. JOHN E. WALKER, J. Infect. Dis. 43:300, 1928.

The course of a laboratory infection with Pfeiffer's bacillus is described. The symptoms consisted of rhinitis, conjunctivitis and bronchitis. There was no fever. Organisms serologically identical with the laboratory strain were isolated from the nose, conjunctivae and sputum. The disease would ordinarily be classified as a severe cold, though the diagnosis of sporadic influenza cannot be entirely eliminated. The infection demonstrates anew that some strains of the organism have an extraordinary avidity for attacking the mucous membrane of the respiratory system as the primary cause of disease.

AUTHOR'S SUMMARY.

STAPHYLOCOCCUS AUREUS CONJUNCTIVITIS OF THE NEW-BORN. ARTHUR B. THOMAS, J. Infect. Dis. 43:306, 1928.

An acute purulent conjunctivitis may occur in infants without evidence of a preexisting vaginitis in the mother. In 100 consecutive cases of purulent conjunctivitis of new-born infants, none appeared to be caused by the gonococcus. Cultures of *Staphylococcus aureus*, isolated from the conjunctivitis and some other lesions that were present, seemed to belong to a single strain and were atypical in staining qualities, metabolic reactions with carbohydrates, and in pathogenicity for animals. This organism was considered to be the causative agent in all the cases and was probably transmitted through contaminated olive oil or boric acid or both.

AUTHOR'S SUMMARY.

CHEMICAL AND BACTERIAL INHIBITION OF GAS FORMATION IN BACTERIAL CULTURES. MITSUTERU ISHIKAWA, J. Infect. Dis. 43:311, 1928.

Subcarbonate, subgallate, nitrate, subnitrate of bismuth, ammonium and sodium benzoates, potassium bichromate, potassium chlorate, sodium fluoride, sodium iodate, ammonium and sodium nitrates and sodium salicylate definitely suppress the evolution of gas, not only from carbohydrates by single cultures of gas-producing bacilli and by three types of associate cultures (a gas-forming with an acid-producing organism, an aerogenous bacillus with a proteolytic organism, and gas-forming and acid-producing organisms with a proteolytic bacterium), but also from sodium formate by pure cultures of aerogenous bacteria. The inhibitory effect of the paratyphoid bacillus on gas production of the colon bacillus appears to depend, partly at least, on a deficiency of proper nitrogenous substances apparently resulting from the metabolic activity of the paratyphoid bacillus.

AUTHOR'S SUMMARY.

INFLUENCE OF IODIDE ON BACTERIAL DECOMPOSITION OF NITROGENOUS SUBSTANCES. MITSUTERU ISHIKAWA, J. Infect. Dis. 43:321, 1928.

Potassium iodide and potassium iodate exert an inhibitory effect on the formation of ammonia by proteolytic organisms of a gelatin culture and on the production of amino-acids by the proteolytic bacteria-free enzyme. In this effect, potassium iodide has practically no demonstrable selective action; different bacteria are affected almost equally by the presence of the iodide. The liberation of

ammonia from urea by ureasplitting bacteria, cultured or washed, is decreased under the influence of the iodide, apparently, through an inhibitory effect on the activity of the enzymes.

AUTHOR'S SUMMARY.

THE THERMAL DEATH POINT OF *BRUCELLA ABORTUS* IN MILK. RUTH BOAK and C. M. CARPENTER, J. Infect. Dis. **43**:327, 1928.

The thermal death point of eight strains of *Brucella abortus* of porcine, human and bovine origin grown in milk was variable. The porcine strain was most resistant. An exposure of fifteen minutes at 140 F. (60 C.) destroyed the human and bovine cultures that were examined. The porcine strain, however, was still viable at this temperature.

The injection of guinea-pigs was more reliable than cultures for determining the viability of *Brucella abortus* in milk.

AUTHORS' SUMMARY.

CLASSIFICATION OF BACTERIUM ALCALIIGENES, PYOCYANEUM AND FLUORESCENS. BRUNO LEO MONIAS, J. Infect. Dis. **43**:330, 1928.

A microbiologic collection of thirty cultures has been classified systematically on the basis of morphology and of biochemical reactions with special reference to their relationship to two main groups of bacteria, the one group related to *Bacterium coli*, and the other to *Pseudomonas migula*.

AUTHOR'S SUMMARY.

COMPARISON OF GLYCEROL AND BRILLIANT GREEN BILE FOR TREATMENT OF FECES FOR ISOLATION OF TYPHOID ORGANISMS. LEON C. HAVENS and CATHERINE RIDGWAY, J. Infect. Dis. **43**:345, 1928.

Six hundred and sixty-one specimens of feces containing known numbers of typhoid bacilli were inoculated into both 30 per cent glycerol and brilliant green bile. Positive results were obtained in 43 per cent of the specimens in glycerol; and in 75 per cent in brilliant green bile. Dosages of at least 100,000 typhoid bacilli per one-tenth gram of feces are necessary to obtain consistently positive results in glycerol, while one tenth of this number will yield the same percentage of recoveries from brilliant green bile. In glycerol the minimal detectable number of typhoid bacilli in feces appears to be 10,000; in brilliant green bile, 1,000. The effect of the age of the specimen has been studied. Specimens in brilliant green bile show a slight decrease in positive results for forty-eight hours, while the typhoid bacilli in the same specimens in glycerol disappear rapidly.

AUTHORS' SUMMARY.

SEPTIC INFECTION DUE TO BACTERIUM MORGANI L. T. THJÖTTA, J. Infect. Dis. **43**:349, 1928.

A case of septic infection due to *Bacterium morgani* l is reported which originated in the gallbladder and terminated fatally on the twelfth day after the onset of acute symptoms. *B. morgani* l was isolated from the gallbladder and from the blood. The patient's serum agglutinated the organism in a dilution of 1:320. *B. morgani* l is generally considered a nonpathogenic, rare type of *Bacillus coli*, which under certain conditions, may become highly virulent. The generic name, *Salmonella morgani*, is found to be inappropriate. This organism should properly be called either *B. morgani* l, *B. metacoli* or *Escherichia morgani*.

AUTHOR'S SUMMARY.

BACTERIOLOGIC AND BACTERIOPHAGIC STUDY OF INFECTED URINES. JANET ANDERSON CALDWELL, J. Infect. Dis. **43**:353, 1928.

In the classification of 112 cultures of bacilli from infections of the urinary tract, a group of 12 aerobic, gram-negative bacilli which produce spores was

recognized and described. Seventeen cultures related to fluorescent bacilli were also described.

Sewage filtrate produced marked lysis of 74 per cent of the 100 nonspore-forming cultures and failed to produce lysis of 7 per cent. These 100 cultures were classified into colony types on the basis of dissociative changes. The susceptibility of the various dissociative types to lysis by sewage filtrate was tested. The results strongly indicated that there is no stage of dissociation of urinary bacilli which is resistant to bacteriophagic action.

Native bacteriophage could be demonstrated in the filtrates of twenty-six of the 100 urines: in 20, only two passages were required. It can be demonstrated about as often with the organism found in the same urine as by using stock cultures of colon and dysentery bacilli. Native bacteriophage was found associated with every cultural group; with cultures in every stage of dissociation, and with cultures having all degrees of sensitiveness to lysis. Therefore, contact with bacteriophage in the body does not produce in a culture resistance to lysis or any constant change in its growth characteristics, nor does it force the culture into any one stage of the dissociation cycle.

AUTHOR'S SUMMARY.

PRODUCTION OF HISTAMINE, TYRAMINE, BRONCHOSPASTIC AND ARTERIOSPASTIC SUBSTANCES IN BLOOD BROTH BY PURE CULTURES OF MICROORGANISMS. KARL K. KOESSLER, MILTON T. HANKE and MARY S. SHEPPARD, J. Infect. Dis. 43:363, 1928.

This paper contains a report on the production of histamine, tyramine, bronchospastic and arteriospastic substances by 223 micro-organisms grown on a blood-broth medium. Ninety-four are members of the colon-typhoid group. Nine of the organisms convert histidine into histamine; of these, two belong to the *Escherichia* group, and seven to the *Salmonella* group. Five of the eight *Salmonella morganii* strains produce histamine. Tyramine was not produced in this group. The faculty for producing bronchospastic and arteriospastic substances other than histamine is highly developed in the colon-typhoid group of micro-organisms. Of 49 *Salmonella* studied, 38 produced spastic substances; of 6 dysentery *Shiga* studied, 5 were spastic; of 12 paradyseutery studied, 6 were spastic; of 9 *Escherichia* studied, 9 were spastic, and all of the typhoid bacilli studied were spastic. Taken collectively, of the 94 representatives of the colon-typhoid group studied, 67 produced spastic substances.

Bronchospastic and arteriospastic substances are rarely produced by micro-organisms other than those belonging to the colon-typhoid group. Histamine was not produced by any of the 129 micro-organisms that are not members of the colon-typhoid group. Of these 129 micro-organisms, 5, all of them streptococci, produced tyramine.

AUTHORS' SUMMARY.

THE METABOLISM OF LEISHMANIA TROPICA. A. J. SALLE and CARL L. A. SCHMIDT, J. Infect. Dis. 43:378, 1928.

A solid and a liquid medium were prepared for the cultivation of *Leishmania tropica*. The growth on the liquid medium was sufficient for the determination of the metabolic activities of *Leishmania tropica*. The organism was grown on the standard medium and on mediums in which certain described variations were made. The analytic data indicated that the metabolism of *Leishmania tropica* does not differ essentially from that of many bacteria. Carbohydrate exerts a marked sparing action toward the protein of the medium. The organism possesses marked proteolytic powers. Its utilization of protein was demonstrated by an increase in the ammonia content of the medium and a rise in pH . Its utilization of protein was demonstrated also in an increase of split-protein products. Experiments showed that this organism cannot survive under anaerobic conditions. The function of hemoglobin in the medium may be to contribute an accessory factor of food or growth.

AUTHORS' SUMMARY.

INTRANASAL INOCULATIONS OF RABBITS WITH *BACILLUS INFLUENZA*. JOHN E. WALKER, J. Infect. Dis. **43**:385, 1928.

Following the intranasal inoculation of rabbits with a recently isolated strain of Pfeiffer's bacillus, it was possible to recover the organism from the nasal cavities of the animals for periods of from four to fifteen days. Two animals so inoculated showed a nasal discharge at the time when the organisms were most numerous. The inoculation was followed by the appearance of agglutinins in the blood stream. Animals once infected were immune to reinfection. After two months' cultivation, the strain lost its ability to attack the nasal mucous membrane of rabbits. Two other strains of Pfeiffer's bacillus were tested and were found unable to produce infection. Failure to produce disease with Pfeiffer's bacillus is demonstrated experimentally to be due either to immunity of the host as a result of previous infection or to lack of virulence on the part of the organism.

The fluctuations in the virulence of the organism and in the resistance of the host fit in well with what would be expected of the etiologic agent of epidemic influenza. These facts, together with the now well substantiated ability of the organism to produce primary respiratory disease of the cold-influenza type, are believed to relate Pfeiffer's bacillus to the etiology of epidemic influenza more closely than ever.

AUTHOR'S SUMMARY.

MICROORGANISMS OF LUNG ABSCESS AND BRONCHIECTASIS. LUCILLE H. ERMATINGER, J. Infect. Dis. **43**:391, 1928.

The bacteriologic examinations in thirty-three cases of chronic and acute abscess of the lung and bronchiectasis disclosed the pyogenic organism, *Staphylococcus aureus* in 75.4 per cent of the total number of cases, hemolytic streptococci in 55.3 per cent and pneumococci in 19.4 per cent. A spirochete, apparently falling into the *Leptospira* group, according to Noguchi's classification, was obtained from the case reported and was kept alive in a mixed culture containing bacteria, for a period of fourteen days.

AUTHOR'S SUMMARY.

ABSENCE OF INFECTIVITY IN FILTERED URINE FROM DIABETIC PATIENTS.

G. HAROLD ETINGER and GUILFORD B. REED, J. Infect. Dis. **43**:399, 1928.

Fresh urine from diabetic patients, filtered (Berkefeld) and injected into fourteen rabbits and seven dogs, caused no appreciable change in the percentage of blood sugar for periods of from 55 to 236 days. Aerobic and anaerobic cultures had similar negative results during periods up to 63 days. Small amounts of reducing substances were found occasionally in the urine of some of the rabbits, but not in excess of amounts found in the control animals. There was never any suggestion of interference with carbohydrate metabolism.

The urine was obtained from eight patients with diabetes, ranging in age from 12 to 55 years and with histories of diabetes for from three weeks to fifteen months. It may be presumed that if the urine of a diabetic patient contains a causal organism it would be present during this period. The conclusion is that the filtered urine of a patient with diabetes contains no organism which can reproduce the diabetic condition in dogs or rabbits.

AUTHORS' SUMMARY.

GROWTH OF PARAMECIA IN PURE CULTURES OF PATHOGENIC BACTERIA AND IN THE PRESENCE OF SOLUBLE PRODUCTS OF SUCH BACTERIA. CHARLES HUGHES PHILPOTT, J. Morphol. **46**:85, 1928.

Virulent hay-infusion cultures of *Bacillus pyocyaneus* are toxic to pure-line races of three species of paramecia, but these races may acquire a tolerance for this toxic agent. Races with acquired tolerance have been grown for long periods of time in toxic, pure cultures of *B. pyocyaneus* by means of the daily-isolation culture, and here the average division rate is as high as, or higher than, in the chance-mixed bacterial cultures in which these protozoa are usually maintained in

the laboratory. The tolerance is lost, however, when the paramecia are removed from the toxic cultures and grown for a number of generations in cultures of nontoxic bacteria.

The toxic agent that is lethal to paramecia is probably the soluble toxin of *B. pyocyaneus*. The investigation shows that the agent is soluble and either thermolabile or volatile. It also shows that all deleterious substances, other than the soluble toxin, known to be produced in cultures of this bacillus, are nonlethal to paramecia.

Hay-infusion cultures of *Bacillus enteritidis* were lethal to paramecia. All attempts to develop tolerance in paramecia for the toxic agent in these cultures failed.

Under the experimental conditions that prevailed, diphtheria toxin was found to have no appreciable effect on the division rate or death rate in three species of paramecia.

AUTHOR'S SUMMARY.

OBSERVATIONS ON THE GRAM-NEGATIVE COCCI OF THE NASOPHARYNX, WITH A DESCRIPTION OF *NEISSERIA PHARYNGIS*. G. S. WILSON and MURIEL M. SMITH, *J. Path. & Bact.* **31**:597, 1928.

Seventy-eight strains of gram-negative cocci, other than meningococci, have been studied on a series of mediums, and their colonial appearance, growth in serum broth and fermentation reactions noted. On ascitic agar plates after forty-eight hours' incubation the colonies may be divided into smooth and rough types; but after five days many of the primarily smooth colonies undergo a transformation into the rough type. Experiments have shown that one and the same strain may be dissociated into smooth and rough variants, and that smooth variants may be recovered from a pure culture of a rough variant. The growth in serum broth after twenty-four hours is subject to great variation in appearance; but, on the whole, the permanently smooth colonial types give rise to a powdery or finely granular deposit, and the primarily and secondarily rough types to a coarsely granular deposit often accompanied by a surface ring growth. The fermentation reactions have been tested in litmus ascitic agar sugars and in serum peptone water sugars containing Andrade's indicator. In only one half of the fifty strains examined in both mediums were the results in agreement. It is concluded that the cultural and biochemical characters of the gram-negative cocci are subject to such variation that they cannot justifiably be used for purposes of classification in the way in which they have hitherto been employed. It is suggested that instead of dividing them into a number of so-called species *catarrhalis*, *flavus*, *cinereus*, *mucosus* and *siccus*, they should be grouped under the broad term *Neisseria pharyngis*, the characteristics of which are enumerated. It seems possible, in the light of S. P. Wilson's work that within this group there may be subgroups the characteristics of which, though subject to a certain amount of variation, are yet sufficiently constant to allow of their differentiation. Further work, however, is necessary before the delimitation of these subgroups can be laid down.

AUTHORS' SUMMARY.

THE PATHOGENIC VALUES OF PNEUMOCOCCAL TYPES: THE LESIONS PRODUCED IN RELATION TO VIRULENCE. J. F. GASKELL, *J. Path. & Bact.* **31**:613, 1928.

The sequence of lesions produced in the lung with rise of titer is similar with all pneumococci. The pathogenicity of type II strains, however, is lower than that of type I in both mice and rabbits. Not only is it harder to reach a given titer in mice, but the lesions produced at that titer are of lower grade than those produced by type I. The pathogenicity of type III strains is lower for mice, rabbits and man; it is again harder to reach a given titer for mice, and less severe lesions are produced in the lung of the rabbit at that titer than with type I. The pathogenicity of group IV organisms, which are virulent and have been obtained from severe lesions, is, if anything, higher than that of type I. Such organisms are therefore quite as dangerous as type I and as easily raised to a virulent titer.

AUTHOR'S SUMMARY.

HISTAMINE AND INFECTION. G. MARSHALL FINDLAY, J. Path. & Bact. **31**:633, 1928.

It is suggested that the well known relationship between injury and the localization of organisms in injured tissue is due to the liberation by injured tissue of histamine or a histamine-like substance which causes dilatation of the capillaries and increased permeability of the capillary endothelium with the result that organisms present in the blood stream are enabled to escape into the surrounding tissues. Evidence in support of this theory is brought forward in experiments with the viruses of fowl pox, vaccinia and the Rous sarcoma, *Staphylococcus aureus*, streptococcus and pneumococcus.

AUTHOR'S SUMMARY.

A CASE OF ENDOCARDITIS IN MAN, ASSOCIATED WITH *BACILLUS PARAINFLUENZAE*, RIVERS, 1922. DOROTHY S. RUSSELL AND PAUL FILDES, J. Path. & Bact. **31**:651, 1928.

A case has been described in which a subacute infective endocarditis was excited by a bacillus identified as *Bacillus parainfluenzae*, Rivers, 1922. The pathogenicity of the organism has been further established by the demonstration of multiple foci in the myocardium, brain and meninges in which emboli containing collections of these bacilli had lodged in arterioles and capillaries, causing a focal inflammatory reaction and hemorrhage. It is believed that this is the first instance of a causal relationship being demonstrated between this organism and disease in man.

AUTHORS' SUMMARY.

THE TYPES OF TUBERCLE BACILLI IN HUMAN BONE AND JOINT TUBERCULOSIS. A. STANLEY GRIFFITH, J. Path. & Bact. **31**:875, 1928.

Tubercle bacilli have been isolated from 598 cases of tuberculosis of the bones and joints and their type determined. Bovine bacilli were found in 20 per cent of persons of all ages, in 33 per cent of children less than 5 years of age and in 24 per cent of children between the ages of 5 and 10 years. No patient more than 23 years of age yielded bovine bacilli. Bovine bacilli appear to account for a larger proportion of the cases of tuberculosis of the spine than other commonly affected bones and joints. Tuberculosis of bones and joints may be the result of either respiratory or alimentary infection.

AUTHOR'S SUMMARY.

BACILLUS PROTEUS INFECTIONS. JOHN F. TAYLOR, J. Path. & Bact. **31**:897, 1928.

The name *Bacillus proteus* should be restricted to a well defined group of organisms. They are nonsporing, gram-negative, pleomorphic bacilli which produce a spreading or creeping growth on solid mediums. They are proteolytic and hemolytic. They do not ferment lactose mannite or dulcitol, but ferment dextrose and saccharose and occasionally maltose. True indol may or may not be formed from peptone water. In milk, a transient clot is formed which is rapidly peptonized. In this investigation fifty-three strains recovered from human sources were examined by morphologic, cultural, biochemical and serologic methods. All these strains have the aforementioned characteristics. Only three of the strains fermented maltose; these same three strains alone produced true indol. Agglutination tests show variations between strains; absorption tests seem to show definite differences. *B. proteus* may produce severe infection in the human subject or may exist as a harmless saprophyte in the tissues, body fluids or excreta. An attempt has been made to classify the strains as pathogenic or nonpathogenic on the basis of the history, clinical course and bacteriologic observations in each case. Twenty-two strains have been classed as pathogenic, twenty-four as nonpathogenic and seven as doubtful. No classification into pathogenic and nonpathogenic strains could be made by the laboratory methods employed, and no differences were found between strains recovered from urinary, fecal or other sources. *B. proteus* "X 19"

of Weil and Felix was found to be serologically distinct from the fifty-three strains of *B. proteus* collected, but otherwise resembled them closely.

AUTHOR'S SUMMARY.

RESEARCHES ON ANTHRAX INFECTION AND IMMUNITY. D. COMBIESCO, Arch. Roumaines de path. expér. et de Microbiol. 1:81, 1928.

Besredka and others have reported that anthrax infection in animals takes place only through the skin. In this work the possibility of other routes of infection is investigated in rabbits and guinea-pigs.

In the normal animal, the blood leukocytes engulf virulent anthrax bacilli and show negative chemotaxis for encapsulated organisms. In fresh serum, non-encapsulated bacteria undergo lysis, while encapsulated bacteria do not. In hyper-immunized animals, phagocytosis of encapsulated bacilli takes place. The negative chemotaxis for leukocytes that is exercised by encapsulated bacilli in the normal animal is due to the combined action of the capsule and the organism itself. Thus an attenuated bacillus, even though encapsulated, is phagocytosed, as is also a virulent nonencapsulated organism, but phagocytosis of bacilli which are both virulent and encapsulated does not take place.

The skin is not the only organ through which anthrax infection can take place. The experiments show that intravenous injection of bacilli in animals has no effect if the dose is small, less than 1 cm. of emulsion, but with a larger dose, death occurs regularly. The bacteria are not all taken care of by the phagocytes; those that remain rapidly become encapsulated and acquire negative chemotaxis for leukocytes. This process is referred to as animalization. Injection with cultures developed in whole blood or inactivated serum similarly results in death, while those developed in fresh serum undergo lysis and do not cause infection. It is also found possible to infect by inoculating other organs directly, such as the lungs, liver and spleen. Intraperitoneal or subcutaneous inoculations also kill if the bacilli are protected from too rapid phagocytosis, and are given time to undergo animalization. This can be done by introducing them enclosed in capillary tubes open at one end, through an incision into the abdominal cavity or subcutaneous tissues. The tubes are broken at the end of several days, after animalization has occurred and the host dies. The histologic structure of the skin favors infection in a similar manner. A certain number of bacilli in the lacunar spaces of the dermis escape phagocytosis for some time, thus acquiring resistance to destruction. Results similar to these have been obtained by other experimenters.

GUINEA-PIG EXPERIMENTS WITH THE TUBERCULOUS FILTRATES. M. LINDEMANN AND BANG DSCHENG LI, Beitr. z. Klin. d. Tuberk. 70:380, 1928.

Forty-one guinea-pigs were given injections of sterile filtrates from sputum and pure cultures. Five of them developed positive tuberculin reactions. Only in three animals was it possible to demonstrate one acid-fast rod. Whether the acid-fast rods demonstrated were tubercle bacilli or not could not be decided.

MAX PINNER.

NONACIDFAST FORMS IN SAPONIN-GLYCEROL BROTH CULTURES OF THE TUBERCLE BACILLUS. O. KIRCHNER, Beitr. z. Klin. d. Tuberk. 70:385, 1928.

In saponin-containing glycerol broth cultures, nonacid-fast organisms were found. These organisms constituted a strictly specific antigen in complement fixation.

MAX PINNER.

EXPERIMENTAL TUBERCULOSIS IN NORMAL RATS. K. HAGEDORN, Beitr. z. Klin. d. Tuberk. 70:389, 1928.

Rats may be infected by large doses of bovine bacilli. The lesions appear differently than in other animal species. One finds an enlargement of the spleen

and numerous pulmonary foci. The histologic characteristic is the presence of large numbers of foam cells. The infected rats usually do not react to tuberculin, but in the majority of cases their serum gives a positive complement-fixation test.

MAX PINNER.

THE FILTRABILITY OF THE TUBERCULOUS VIRUS. F. RABINOWITSCH-KEMPNER, *Ztschr. f. Tuberk.* **52**:18, 1928.

One hundred and forty-six guinea-pigs received injections of filtrates from various tuberculous materials including pure cultures, sputum and exudates. Six of these animals developed generalized tuberculosis. In all six cases, the material was filtered through a membrane filter. All filtrates filtered through Chamberland filters did not produce tuberculosis. All cultures with filtrates remained sterile. In no case was it possible to demonstrate acid-fast rods in the glands or organs of healthy noninoculated animals. It must be assumed that the acid-fast rod is not the only shape of the tubercle bacillus. Under certain circumstances the development of the classic shape does not occur, but a microscopically invisible type develops the culture of which has so far not been successful. The virulence of this type must be low. A further report will deal with the conditions under which the typical type or filtrable virus develops.

MAX PINNER.

Immunology

THE COMPLEMENTING PROPERTIES OF BLOOD PLASMA. ROSCOE R. HYDE, *Am. J. Hyg.* **8**:859, 1928.

A potent complement has been found in the blood plasma of a hemophiliac subject. It has also been demonstrated in other blood plasma which has been prevented from clotting by the use of heparin. In both cases the titer of the complement in the plasma was the same as in the serum from the same blood after clotting had occurred. These and other observations, for which experiments are described, demonstrate that complement must occur normally in the circulating blood, that it is not changed by the clotting of the blood or by injury of phagocytes and that it is a natural and not "an artificial principle" as claimed by d'Herelle.

PEARL ZEEK.

PRECIPITIN REACTIONS WITH VARIOUS TISSUES OF ASCARIS LUMBRICOIDES AND RELATED HELMINTHS. GRAEME A. CANNING, *Am. J. Hyg.* **9**:207, 1929.

The data presented here indicate that certain isolated tissues, due to their composition and embryonic origin, are preeminently fitted to use in performing immunologic tests to trace biologic relationships of animals, whereas others not only are unsuitable but would tend to confuse the results. Thus, more delicate specific differences may be discovered between various ascarids by the use of a substance, like the egg, whereas more distant relations may be revealed by the use of sperm. From these things it follows that it is far better to find the most suitable tissue than to use the whole worm when conflicting elements would obscure the results.

FROM AUTHOR'S SUMMARY.

IMMUNIZATION WITH R. PNEUMOCOCCI. W. S. TILLET, *J. Exper. Med.* **48**:791, 1928.

A broad immunity against infection with virulent *S. pneumococci* (Types I, II, III) can be induced in rabbits by vaccination with the degraded R. strains of pneumococcus. This form of active resistance is effective in the absence of demonstrable type-specific antibodies, and may be passively transferred to normal rabbits by the blood of the immunized animal.

AUTHOR'S SUMMARY.

THE MODE OF ACTION OF A VIRICIDAL SERUM. S. P. BEDSON, Brit. J. Exper. Path. **9**:235, 1928.

Experiments are cited which warrant the conclusion that virus and neutralizing antibody unite in vitro.

PEARL ZEEK.

DILUTION PHENOMENON OBSERVED IN THE TITRATION OF THE SERUM OF FOWLS IMMUNIZED AGAINST THE VIRUS OF FOWL PLAGUE. CHARLES TODD, Brit. J. Exper. Path. **9**:244, 1928.

1. A mixture of fowl plague virus with the corresponding immune serum, so prepared as to be just nonvirulent when injected intramuscularly into a fowl, is rendered virulent by simple dilution with saline.

2. This dilution phenomenon takes place even after the undiluted mixture has been kept at 37 C. for four hours, showing that the action of the immune serum is not that of destroying the virus in vitro, but that the virus and immune bodies can exist side by side in the mixture without destruction of the former.

3. Similarly, a mixture of the virus with just enough immune serum to render the mixture harmless to fowls when injected intramuscularly is found on intravenous injection to give rise to acute fowl plague, although the fowl is apparently not more susceptible to intravenous than to intramuscular injection of the virus.

4. This behavior of mixtures of the virus with its immune serum resembles the behavior of toxin-antitoxin mixtures observed in the case of tetanus, diphtheria and certain other toxins.

5. The dilution phenomenon is of practical importance in the titration of immune serums against the corresponding viruses, as the degree of dilution of the infected mixture may, within certain limits, influence the result of the injection.

AUTHOR'S SUMMARY.

EXPERIMENTS ON THE PURIFICATION AND CONCENTRATION OF SCARLET FEVER TOXIN. PERCIVAL HARTLEY, Brit. J. Exper. Path. **9**:259, 1928.

Crude scarlet fever toxin was purified and concentrated by Walpole's method, and the active principle, which gives the characteristic skin reaction, was obtained in a highly purified and concentrated form. This may possibly be a step toward the standardization of scarlet fever antitoxin, using this concentrated product as test toxin and the rabbit as biologic indicator.

PEARL ZEEK.

CONCENTRATION AND PURIFICATION OF STREPTOCOCCAL TOXIN. J. V. PULVERTAFT, Brit. J. Exper. Path. **9**:276, 1928.

Filtrates from cultures of the Dochez strain of *Streptococcus scarlatinae* were prepared which were fatal for rabbits in doses of from 2.5 to 10 cc. A method is described by which the toxin may be so purified and concentrated as to be lethal in doses as small as 0.1 cc. Complete protection is afforded to rabbits against large doses of the toxin by streptococcal antitoxic serum, but tetanus and diphtheria antitoxins and normal horse serum have no effect.

PEARL ZEEK.

EXPERIMENTAL RESEARCHES ON THE NECROTIC LESIONS PROVOKED BY THE INJECTION OF MASSIVE DOSES OF B.C.G. M. J. ZEYLAND and MME. E. PIASECKA-ZEYLAND, Ann. de l'Inst. Pasteur **42**:652, 1928.

Rabbits and guinea-pigs were injected with 15 or 20 mg. of B.C.G. or with killed virulent tubercle bacilli by various routes, intravenous, intra-arterial, intracardiac, intrapleural, intraperitoneal and intrarenal. Rabbits injected intravenously gave noncaseous follicles. Guinea-pigs injected intraperitoneally showed

tubercles, sometimes caseous. Part of the rabbits given an intracardiac injection and all given injections in the pleura or in the kidney gave tubercles with necrosis. Necrotic lesions are secured experimentally when conditions permit an agglomeration of bacilli in the tissues. This necrosis is due to endotoxins comparable to those of some of the acid-fast saprophytes. "Under the conditions of vaccination, B.C.G. is inoffensive."

M. S. MARSHALL.

RESEARCHES ON SERUM ANAPHYLAXIS. E. SUAREZ, *Ann. de l'Inst. Pasteur* **42:877**, 1928.

Euglobulin, pseudoglobulin and serum albumin act as different antigens; each sensitizes specifically and is toxic for animals sensitized with whole serum and with corresponding antigen. The specificity of the neighboring fractions (pseudoglobulin-euglobulin, pseudoglobulin-serum albumin) is such that animals sensitized with one fraction resist from ten to fifteen lethal doses of the other fraction. The specificity of the less related fractions (euglobulin-serum albumin) is such that animals sensitized with one resist from fifteen to eighty lethal doses of the other. These antigens sensitize after different periods of incubation. The minimum (nine to twelve days) proper for serum anaphylaxis is reduced in euglobulin anaphylaxis to from three to six days; it is from twelve to fourteen days in serum-albumin anaphylaxis, and from eight to ten days in pseudoglobulin anaphylaxis.

AUTHORS' RÉSUMÉ.

REINFECTION OF TUBERCULOUS GUINEA-PIGS AND GUINEA-PIGS IMMUNIZED WITH B.C.G. M. E. RIST and Mlle. J. MISIEWICZ, *Ann. de l'Inst. Pasteur* **42:945**, 1928.

Virulent tubercle bacilli were inoculated subcutaneously or into the inguinal glands of a group of guinea-pigs, the survivors being used for reinfection. All of another group inoculated with B.C.G. survived. All reinoculations were intraperitoneal in varying amounts. In general, the results indicate that animals surviving virulent tubercle bacilli on reinoculation die sooner than the control animals—possibly a matter of allergy—whereas animals injected with B.C.G. survived the second inoculation (virulent tubercle bacilli) longer than those in the control group.

M. S. MARSHALL.

RESEARCHES ON SERUM ANAPHYLAXIS. E. SUAREZ and W. SCHAEFFER, *Ann. de l'Inst. Pasteur* **42:1447**, 1928.

One may obtain regularly anti-anaphylaxis without shock; in this case, anti-anaphylaxis is more intense than that following shock. One may obtain repeated shock (pure euglobulin) without having anti-anaphylaxis. Between shock and anti-anaphylaxis there exists no relation of cause and effect; it is a question of concomitant phenomena capable of being dissociated. Researches carried on with anaphylaxis and anti-anaphylaxis of various proteins of serum enable us to state that each of these is constituted of two groups of functions; sensitizing and toxic on one hand and anti-anaphylactic on the other hand. These functions are not equally represented in each of the serum proteins. The euglobulin is especially sensitizing and toxic; the anti-anaphylactic properties are insignificant or nil. In the pseudoglobulin both functions are represented as in the whole serum. The serum albumin possesses more anti-anaphylactic properties than toxic and sensitizing properties. The toxic and sensitizing properties are strictly specific for each antigen; the anti-anaphylactic properties are common to several fractions of serum. A heterologous fraction produced a better anti-anaphylaxis than a homologous fraction, the former requiring a heavier dose in injection than the latter.

AUTHORS' SUMMARY.

THE RELATIONSHIP BETWEEN STRUCTURE AND FUNCTION OF LIPOID ANTIGENS. H. SACHS and G. BOCK, *Arb.a.d.Staats-Inst. f. exper. Therap.* **21**: 159, 1928.

Slow, fractional dilution of lipoidal extracts proved essential for their antigenic function in complement fixation. The quickly diluted extracts not only failed to fix complement but actually inhibited—by reaction as a “half haptene” with positive serums—the complement fixation otherwise produced by these serums with properly diluted extract. This inhibition was attributed to the state of fine dispersion of the lipid in suspension. Alcoholic extracts of guinea-pig kidney tested with rabbit antisera for the kidney extracts plus swine serum, and cholesterolized beef heart extract tested with Wassermann-positive serums from human beings were among the combinations tried in these tests.

ETHEL B. PERRY.

CHEMOSPECIFIC ANTIGENS. A. KLOPSTOCK and G. E. SELTER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**: 118 and 450, 1928.

Diazotized serums may be used as antigens, in which case the resulting antisera lose their species specificity almost completely and acquire a specificity for similarly diazotized serums from various species. Complex antigens prepared by treating serum with diazotized atoxyl or metanilic acid likewise yield antisera which give specific precipitin and complement-fixation reactions with serums from various sources treated with the same chemical compound. In these cases, addition of the simple chemical compound prevents the reaction of antigen and antiserum in the complement-fixation reaction.

Simple mixtures of serum and diazotized atoxyl may be used for active immunization, in which case the resulting antisera are strongly specific for the atoxyl, although they may also exhibit species specificity or even both types of specificity. The loss in species specificity of the complex antigens prepared by Landsteiner's method is due to the drastic treatment of the serum with acid, alkali and alcohol rather than to the formation of a compound with a new specificity for the added chemical group.

ARTHUR G. COLE.

THE EFFECT OF SERUM ON THE ISOLATED VESSEL. P. INTROZZI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**: 167, 1928.

Introzzi continued the experiments of Friedberger on the constricting effect of normal, homologous and heterologous serum (rabbit, guinea-pig, rat, frog, carp, beef) on the isolated blood vessel of the guinea-pig, rabbit and rat. The constricting substances were present in the insoluble fraction of the albumin obtained by electro-osmosis. The irradiation of normal serum with ultraviolet rays caused a decrease or complete disappearance of the constricting principle. The vasoconstricting effect was not influenced by the state of digestion or starvation of the animal when the serum was obtained. The serum of tuberculous patients produced irregularly constriction of the isolated vessel of tuberculous guinea-pigs. Similar experiments with the urine of tuberculous persons gave negative results.

W. C. HUEPER.

ANAPHYLAXIS OF ISOLATED VESSELS. E. FRIEDBERGER and P. INTROZZI, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**: 226, 1928.

Using isolated sensitized vessel it was found that the antigenic serum loses its stimulating effect after heating at 100 C. for thirty minutes, but is not demonstrably changed by irradiation with ultraviolet rays. The addition of eosin to the serum before irradiation does not change this result. Isolated vessels of guinea-pigs treated with sheep serum react more markedly on injection of the soluble fraction of albumin and euglobulin than of pseudoglobulin and the insoluble fraction of albumin. Passive immunity can be demonstrated on the isolated vessel of guinea-pigs and rats.

W. C. HUEPER.

SKIN SENSITIZATION AS A MEANS OF STUDYING THE RELATIONS OF DIFFERENT SPECIES. H. FRÖLICH, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:236, 1928.

After a review of the methods for demonstrating biologic relations among different species of animals, the author reports his results from the intracutaneous sensitization of human skin as a method of differentiation. He tested the serum of (1) *Macacus rhesus* and *Macacus cynomolgus*, (2) beef, goat and sheep, (3) rabbit and guinea-pig, (4) white rat and white mouse, (5) chicken, pigeon, goose and turkey, (6) horse, mule and donkey and (7) pike, tench and bream. Biologic relations were established by this method among the animals in the different groups with the exception of those in groups 3 and 7. He succeeded in sensitizing the human skin against the serum of the lower monkeys. His results substantiated the results with other methods.

W. C. HUEPER.

THE PRODUCTION OF PRECIPITATING ANTISERUM OF HIGH VALENCE. GAEHTGENS, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:258, 1928.

The author attempted to further the production of highly effective precipitating serum by the injection of India ink, but the results were favorable only in a small portion of the rabbits. Specific precipitation could be intensified and hastened by lipoids. As lipoids might also intensify the antigenic effect of proteins, rabbits were given injections of mixtures of alcoholic extracts of meat and lipoids. Antiserum with a titer of 1:20,000 were obtained in 94 per cent of the animals. Thorough immunization of rabbits with serum and heterologous lipid antiserum fit for use could be produced in only about 50 per cent. To exclude the effect of lipid in the injected serum, the serum was treated with ether. The use of such purified serum did not always prevent the production of nonspecific precipitins. Good results were obtained with dried serum after removal of the lipoids by alcohol extraction. Dried serum thus treated combined with heterologous lipoids produced in general more species-specific precipitins than dried serum with homologous lipoids.

W. C. HUEPER.

PREVENTIVE IMMUNIZATION AGAINST CHOLERA WITH TOXOIDS. R. KRAUS and N. KOVACS, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:316, 1928.

The injection into rabbits and guinea-pigs of cultures of cholera vibrios to which a diluted solution of formaldehyde U.S.P. (1:0.5) has been added at 37 C., induces resistance to cholera toxins and cultures. Such cholera toxoids proved harmless to persons who responded by producing cholera agglutinins.

W. C. HUEPER.

THE SEROLOGIC REACTIONS OF EXTRACTS OF TAPEWORMS. H. SÄCHS and A. KLOPFSTOCK, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:341, 1928.

Water extracts of tapeworms, when injected into rabbits, lead to the formation of protein and lipid complement-fixing antibodies. Alcohol extracts of tapeworms are antigenic only when they are first mixed with protein, as hog serum, in which case the resulting antisera give strong reactions for the lipid. These antisera also react with other organ lipoids, but not with lecithin. A lecithin antiserum, however, reacts with the tapeworm extract. The tapeworm extract is thus considered to contain specific as well as nonspecific lipid antigens.

ARTHUR G. COLE.

THE IMMUNITY OF SYPHILIS IN RABBITS. P. UHLENHUTH and H. GROSSMANN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:380, 1928.

A spontaneous cure in rabbits from syphilis does not seem to occur. The disease becomes only latent. This conception is supported by the negative result

of a testicular reinfection and the positive results from inoculation with lymph nodes and tissue of other organs of infected animals. Infected rabbits treated in an advanced stage with neosilver arsphenamine and atoxyl acid bismuth showed the existence and the persistence of an active immunity in spite of any evidence of a latent infection as demonstrated by the negative inoculation of other animals with lymph nodes and by the negative result of testicular reinfections. Immunization against syphilis is a slow process as animals are susceptible to reinfection during an early stage of the disease. During the later stages the spirochetes adapt themselves to the immune organism. Animals cured at an early stage by chemotherapy are susceptible to reinfection. The antibodies against spirochetes are mainly bound to the cells. The results in rabbits cannot be applied without modifications and restrictions to syphilis in human beings.

W. C. HUEPER.

THE FERMENTOCYTIC [LIPOLYTIC] REACTION OF THE ORGANISM. M. J. AKSJANZEW, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:423, 1928.

Rabbits and guinea-pigs after injection of neutral fats presented a lymphocytosis, occasionally reaching 95 per cent, an increase of the lipolytic index of the serum, and after a brief temporary decrease during the negative phase an absolute leukocytosis reaching 30 per cent in some cases. The lipolytic ferments are apparently freed on the decomposition of the lymphocytes. The introduction of substances not containing lipoids do not produce lymphocytosis and increase in the lipolytic ferments, rather a decrease. Rabbits with high lymphocytosis and lipolytic index anesthetized with ether, a lipolytic substance, show a rapid increase in the lipolytic ferments and a simultaneous decrease of lymphocytes. The author asserts that in diseases showing an active reaction of the lymphopoietic organs the lipolytic ferments and the lymphocytes play an important part and are of diagnostic, prognostic and therapeutic significance. The fat and lipid therapy of tuberculosis is referred to in this connection. Lymphocytes are apparently destroyed by the introduction of fat soluble substances as ether, because degenerated lymphocytes were seen in the blood after such procedures.

W. C. HUEPER.

THE SKIN IN IMMUNITY. E. URBACH, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:471, 1928.

The nonspecific reactivity of the skin, that is its quality to produce nonspecific antibodies, is the result of a phylogenetic adaptation. This function is used therapeutically (sun, water, air-baths, massage, etc.). The specific allergy of the skin is usually due to an acquired specific sensitization. There exist close relations between both, as a strong nonspecific reactivity increases the specific defensive forces of the skin. The specific allergy of the skin depends on the formation of specific cutaneous antibodies. They were demonstrated by other authors by successful passive transmission of the cutaneous hypersensitiveness (graft of sensitized skin, injection of serum of cutaneous vesicles). The latter method is regarded as superior to the blood serum method of Prausnitz-Küstner as the specific character of this test is considered as dubious. The demonstration of specific cutaneous antibodies explains the diagnostic value of the cutaneous reactions and the success of those therapeutic procedures in which living virus of lowered vitality is introduced as an antigen into the most superficial layers of the skin. The employment of the percutaneous method in favor to the intradermal one is recommended for diagnostic and therapeutic purposes. Its advantages consist in simpler technic, less subjective symptoms, no anaphylaxis, almost no local reaction and especially the use of the production of specific and nonspecific epidermal antibodies. Epidermis (Langhans' cells) and cutis (vascular endothelial cells) possess the quality to form antibodies. The constitutional disposition of the epidermis and papillary vessels, respectively, and not the chemical character of the antigen determine the place of action of the allergen.

W. C. HUEPER.

THE EFFECT OF CYTOTOXIC ANTISERUM IN VITRO. R. KIMURA, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **55**:501, 1928.

Rabbits treated with tissue pulp of chicken embryos produce a cytotoxin against chicken cells. When such antiserum is added to cultures of embryonal and adult cells of chicken, it inhibits their growth. The presence of a complement is not necessary for this action. Heat and storage impair its efficacy. It is species-specific as it does not act on cells of rabbit and mouse, and it is almost organ-specific after injection of brain pulp.

W. C. HUEPER.

THE ETIOLOGY AND PATHOLOGIC ANATOMY OF REACTIONS AFTER TRANSFUSION OF BLOOD. ARVID LINDAU, *Acta path. et microbiol. Scandinav.* **5**:382, 1928.

This article gives a review of the literature on unfavorable reactions following transfusion, with reports of three illustrative cases studied by the author. The severe reactions depend on the transfusion of incompatible blood followed by hemolysis. The principal lesions develop in the kidneys and liver, and in certain cases also in the intestine. The lesions in the kidneys and the necroses in the liver are microscopically characteristic.

PNEUMOCOCCUS IMMUNIZATION BY INTRATRACHEAL ROUTE. H. NAKAJIMA, *Scientific Reports Government Instit. Inf. Dis.* **6**:97, 1927.

Successive intratracheal inoculation of rabbits with killed or live pneumococcus cultures produced agglutinins of low titer in the blood. Rabbits thus immunized are protected from pneumococcus septicemia when virulent organisms are injected intravenously, but are not protected against pneumonia.

E. P. JORDAN.

ON THE FORMATION OF ANTIBODIES BY MIXED IMMUNIZATIONS. K. TANAKA, *Scientific Reports Government Instit. Inf. Dis.* **6**:119, 1927.

Experiments with mixed immunization using two different bacilli indicated that the antibodies of both were increased. But antibodies to cholera bacilli were diminished by attempted immunization with cholera bacilli and horse serum.

E. P. JORDAN.

ON THE ANTIGENIC SPECIFICITY OF EPITHELIAL CELLS. K. TANAKA, *Scientific Reports Government Instit. Inf. Dis.* **6**:139, 1927.

The author supplements his previous work on tissue specificity concluding as a result of his experiments that lung tissue is serologically close to spleen and different from liver, muscle tissue, and the mucosa of the alimentary tract. He also concludes that the stomach mucosa and the testicular tissue have a high degree of organ specificity.

E. P. JORDAN.

Tumors

PRIMARY MULTIPLE HEMANGIOMA OF THE SPLEEN WITH MULTIPLE LIVER METASTASES. ARTHUR W. WRIGHT, *Am. J. Path.* **4**:507, 1928.

There is here described a case of primary malignant hemangioma of the spleen which metastasized to the liver, with the production of innumerable tumor masses in that organ. The type cell is the endothelial cell, and the tumor and its metastases are characterized by the formation of blood vessels and blood-filled spaces. The latter are of atypical and unusual appearance. They exist as small or large, cystlike vascular cavities into which they project varying numbers of remarkable papillary processes which are covered with rapidly growing endothelial cells. These processes differ from any structures previously described. Neoplastic growth in these foci is active, malignant and invasive. Alternating with the regions of rapid

and atypical growth there are other foci in which typical blood vessel formation is more evident. Here neoplastic activity is diminished or quiescent, and marked sclerosis is present. In these areas the growth assumes the form of fibrosed hemangiomas. The tumor is remarkable for its rapid, invasive growth, its unusual histologic structure and the formation of multiple metastases. A review of the literature concerning other cases of malignant, metastasizing hemangioma is given.

AUTHOR'S SUMMARY.

PRIMARY CARCINOMA OF THE LIVER: TWO CASES IN CATTLE. WILLIAM H. FELDMAN, *Am. J. Path.* **4**:593, 1928.

From a review of the literature one must conclude that primary carcinoma of the liver is not one of the common tumors of the lower animals. Of the domesticated species the dog seems to be the most often affected. The tumors have also been reported in the following species: horse, cattle, sheep, cat, hog, woodchuck and chicken. In one series reported by Trotter, 119 cases were found in 39,704 necropsies on cattle. The true primary carcinoma of the liver arises from the parenchymatous hepatic cell, and while the tumor is occasionally extremely malignant, it usually exerts its major influence on the hepatic substance in which it arises, metastasis being the exception rather than the rule. Two original cases of primary carcinoma of the liver are reported, both occurring in cattle. Metastasis was not observed in either case.

AUTHOR'S SUMMARY.

ADENOMA AND CARCINOMA OF THE THYROID. FREDERICK A. COLLIER, J. A. M. A. **92**:457, 1929.

Endemic goiters developed carcinoma in 4 per cent. In most of the cases the carcinoma was not suspected before operation. Of 90 cases, 28 per cent concerned medullary carcinoma, 66 per cent aden. carcinoma and 5.5 per cent scirrhus carcinoma.

THE NATURE OF THE CARCINOGENIC AGENTS IN MINERAL OILS. C. C. TWORT and J. D. FULTON, *J. Path. & Bact.* **32**:149, 1929.

In fractional distillation of carcinogenic oils the active agent is sometimes concentrated in the higher, sometimes in the lower fraction. The active agent is concentrated in extracts made with methyl sulphite or methyl sulphate and picric acid, and the process is useful in testing oils intended for industrial use. There is no evidence that carcinogenic substances are made by fractional distillation or by the processes of extraction used. The carcinogenic activity of an oil is much reduced or completely removed by extraction with sulphuric acid, by oxidation and by reduction.

AUTHORS' SUMMARY.

OBSERVATIONS ON INTRACEREBRAL GRAFTS OF HOMOLOGOUS AND HETEROLOGOUS TUMORS. E. HARDE, *Ann. de l'Inst. Pasteur* **42**:1259, 1928.

Of twelve susceptible rats, grafts into the brain of a homologous sarcoma gave ten positive results. A series of rats of a race naturally refractory gave practically no positive results with a rat tumor. Nineteen white mice gave sixteen positive results with a mouse sarcoma. A mouse sarcoma grafted on seven susceptible rats gave four tumors. The same tumor on fourteen rats gave seven successful grafts. A mouse tumor was implanted on a guinea-pig one time out of six. "The rarity of stroma in the tumor at the end of its development, the absence of conjunctival capsule, the abundance of vessels, some areas of necrosis and sometimes the presence of a strong lymphocyte and perivascular reaction in certain points of the periphery of the heterologous grafts or else in the cases of resistant animals; finally the lymphocyte perivascular cylinders at a distance from the tumor" were noted microscopically.

FROM THE AUTHOR'S SUMMARY.

THE PRESENT DAY ORIENTATION ON THE IDEAS OF CANCER. SOME DISPUTED POINTS ON THE ETIOLOGY OF CANCER. TISSUE CULTURES AND THEIR APPLICATION TO THE STUDY OF CANCER. LEAD IN THE TREATMENT OF CANCER; THE FREQUENCY OF CANCER AFTER RECENT MORTALITY STATISTICS. G. ROUSSY, R. LEROUX, M. WOLF, A. HÉRAUX and SIMONE LABORDE, *Ann. de méd.* **24**:345, 396, 411, 419, 1928.

The enumerated articles represent a scholarly review and a discussion on the problems of cancer as they stand at the present time.

B. M. FRIED.

CONCERNING THE SARCOMA OF ROUS AND RECENT EXPERIMENTS BY CARREL. H. T. DEELMAN, *Ann. de méd.* **24**:360, 1928.

Carrel stated that he was able to cause a new growth by injecting into a chicken a mixture of arsenic with the chick embryo pulp. Deelman failed to repeat Carrel's experiments. He then reports his experiments with mixture of Rous' sarcoma and embryonic pulp. Here he was able to corroborate observations made by others that such a combination increases the malignant power of Rous' virus. He believes that the "cellular juice" are responsible for this phenomena; the virus of Rous is attracted by the living embryonic cells thus freeing the fluid from it. In a living animal things happen then in this way: the "agent" of Rous which is able to "multiply" outside of the cell is attracted by the living cells. When the neoplastic cells undergo necrosis the virus becomes free and contaminates the surrounding healthy cells. The tumor grows rapidly because of the rapid division of the cells.

B. M. FRIED.

DEVELOPMENT OF ADENOCARCINOMA OF RATS VARIOUSLY TREATED. G. MENDOLA and C. LORETO, *Tumori* **2**:549, 1928.

On the basis of experiments the authors conclude that the antiblastomatic action of autolysates and of extracts of homologous tumors is not destroyed by ultrafiltration through a Chamberland L⁵ filter. They did not find any specific antiblastomatic immune bodies in the serum of rats that carried tumors.

W. OPHÜLS.

THE CONNECTIVE TISSUE TUMORS OF THE ABDOMINAL WALL. ONOFRIO ANGELELLI, *Tumori* **2**:594, 1928.

Six cases of fibroma and fibrosarcoma of the abdominal wall are described with review of the pathogenesis, the pathologic anatomy, the symptomatology, the differential diagnosis, the prognosis and the treatment of these tumors.

W. OPHÜLS.

ANTIBODY FORMATION AGAINST INOCULATION CARCINOMA IN THE MOUSE. K. YAMAGIWA, S. TSUKAHARA and S. MORIMOTO, *Virchows Arch. f. path. Anat.* **267**:17, 1928.

The authors were able to show that growth of inoculated carcinomas in mice could be inhibited by injecting extract of spleen from rabbits which had been previously treated with emulsion of mammary carcinoma from mice. In some instances, retrogression of a preexisting tumor took place. This discovery indicates the formation of an antibody for mammary carcinoma of mice in the spleen of rabbits treated with an emulsion of the corresponding tumor. The activity of the splenic extract was much diminished after two weeks, and so had to be freshly prepared.

B. R. LOVETT.

EXPERIMENTAL PRODUCTION OF TERATOMAS OF THE TESTIS IN THE COCK. I. MICHALOWSKY, *Virchows Arch. f. path. Anat.* **267**:27, 1928.

There are two main theories of the origin of the solid teratomas found in the ovary or testis, and containing embryonic tissue from all three germ layers. According to the blastomere theory, the tumor arises from a blastomere split-off

during the early development of the organism. According to the theory of Wilms, Pfannenstiel, and others, cells of the sex glands have the power of developing these tumors. The author injected 5 per cent solution of zinc chlorate into the testicles of cocks, and in this way was able to produce typical teratomas 9 times out of about 200 operations. The tumors were found from two to three months after injection. Other conditions necessary for the development of the tumors could not be determined, but a transitional stage occurred in which collections of cells of the sperm-forming type were observed lying between the canals. The setting free of these cells into the interstitial tissue and their growth there seemed to be a *sine qua non* for the tumor formation. The author concludes that the sperm cells of the cock, like egg cells, have the power of growing into different kinds of tissue under certain conditions. His results favor the theory of growth of teratomas from the sex gland elements.

B. R. LOVETT.

Medicolegal Pathology

BACTERIOLOGY IN CONNECTION WITH FORENSIC MEDICINE. ROBERT DONALDSON, *J. State Med.* **36**:497, 1928.

There is a period elapsing between death and the onset of putrefactive changes during which pathogenic organisms that may have established themselves in the blood may be recovered in culture, if suitable precautions are taken. This period, under average mortuary conditions, in temperate climates may be as long as thirty-six, forty-eight or more hours post mortem. The blood should be collected from one of the peripheral veins, preferably from the femoral, before the body is opened and, in addition, from the right and left sides of the heart. Such bacteriologic examinations may yield information of considerable medicolegal value concerning the cause of death, especially in cases of sudden or unexpected death and in cases in which, during life, the diagnosis has been obscure. It is of further value in that it may throw fresh light on the mechanism by which death was brought about, especially when chronic disease was known to exist.

AUTHOR'S SUMMARY.

GLASSBLOWERS' CATARACT. H. ERGGELET, *Ber. ü. d. 46 Zusammenkunft d. deutsch. ophth. Gesellsch.* **46**:234, 1927.

The eyes of 131 laborers in the glass factories of Jena and Llimenau were examined. In three, minimal opacities, punctiform and minute foci like soap suds in appearance, were found in the polar regions of the lenses. The only real cataracts were in two laborers already pensioned. Only 37 of the 131 laborers were over 45 years of age. Another factor in the low incidence of cataract was the absence of green glass, among the products manufactured. Green glass is said to be especially productive of cataracts.

E. R. LE COUNT.

UNUSUAL CORONARY OCCLUSIONS. G. SCHMIDT, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **11**:380, 1928.

The left coronary artery is more commonly obstructed when abrupt death results from lack of sufficient blood to the heart muscle from occlusion of the coronary arteries. Two sudden deaths in persons apparently well are reported by Schmidt, both from plugging of the right coronary artery at its mouth. In one, the obturating mass was a polypus clot washed in during diastole. From an inflammation of the aortic valves, a mural endocarditis of the aorta by implantation had developed. Subsequently the valvular process had healed, and a polyp of partly organized fibrin remained attached to the lining of the aorta root. The free end of this finally was carried into the mouth of the right coronary artery and blocked it firmly.

The other death was similar, but the polyp was fast to one of the aortic leaflets, and the free end was carried into the mouth of the artery during systole.

E. R. LE COUNT.

DEMONSTRABLE DISEASE OF THE BRAIN IN EXHUMED BODIES. W. WEIMANN,
Deutsche Ztschr. f. d. ges. gerichtl. Med. 11:388, 1928.

Embalming of the dead is uncommon in European countries. As a consequence the changes ensuing in, and the conditions which determine postmortem decomposition, as well as the information which can be obtained by examining bodies in varying stages of putrefaction, have been subjects of frequent comment in foreign journals of legal medicine. It has been ascertained, for example, that the connective tissue stroma of organs resists decomposition for a long time, that epithelium of all sorts quickly disintegrates, especially if highly differentiated, and that putrefaction in the brain is slow. This last-mentioned fact is believed to be due to the large quantity of lipoids in the brain.

There is one record of maintenance of the contour of the brain in a body after thirty-seven years of burial. Gross lesions such as contusions, apoplexy and sclerosis of cerebral vessels are easily found, although not invariably, long after death. The myelin sheaths of nerves and ganglion cells are easily found microscopically even when the brain is semifluid from decomposition. Ganglion cells have been found scattered about on surrounding objects as a result of crushing injuries of the head, long after the tissue has dried. They have also been found after the brain tissue has been burned or desiccated with heat.

Fischer, in Prague, experimenting with the brain tissue of patients with senile dementia and general paresis, found characteristic changes microscopically when the material had been kept from two to three weeks at 12 to 14 C. The report by Weimann is similar: the lesions of paresis were demonstrated in a brain twelve days after death, the organ having been put into formaldehyde promptly at the time of exhumation. Of course, when bodies are embalmed before burial, a microscopic examination of the brain is always essential, even though exhumation is months or years after burial.

E. R. LE COUNT.

TRAUMATIC INTRACRANIAL LACERATION OF NORMAL VERTEBRAL ARTERIES.
K. WOLFF, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 11:464, 1928.

During recent years there has been gradual acceptance of the view that traumatic intraleptomeningeal and subdural hemorrhage of venous origin may occur without either fracture of the cranial bones or bruising of the brain; also that such hemorrhages may cause death quickly. The brain is frequently so covered with blood that the convolutions are almost invisible. The actual site of bleeding is not found, as a rule. Fatal hemorrhages of this kind are not uncommon.

Similar traumatic hemorrhages from traumatic lacerations of large intracranial arteries also occur, but they are rare. They also may happen without contusion of the brain or fractured bones. There are only about four reports of such occurrences. Wolff reviews them all briefly and adds one case from his own experience. In some of the cases there are ruptures of the basilar artery, in others of the vertebral artery and in one, that of a man, aged 71, there is a torn pial artery. One of the basilar tears, incomplete, was 7 mm. long; the adventitia was intact, the artery channel thrombosed and the wall free from disease. In another case there had been hypertrophy of the heart which weighed 470 Gm.; increased blood pressure may have played a rôle. Death takes place quickly when the tear is all the way through the vessel wall. The hemorrhage spreads around the outside of the brain, distends the fourth ventricle and extends into the other ventricles.

Where the vertebral arteries emerge from the atlanto-occipital membrane they are fixed firmly. Crossing the subdural loose tissues of the leptomeninges, they come to lie against the rigid clivus of the occipital bony plate. It is believed that falls which turn the head suddenly to one side may kink the vertebral or basilar arteries in these portions of their course where they lie relatively free; the walls are torn by compression by bone outside, and the incompressible fluid inside is unable to move along in the channel because the vessel is kinked. The

tears, moreover, are ventral. It will be recalled that trauma has been offered as an explanation for aneurysms of these vessels. It has been suggested that the basilar artery, for example, may be bruised against the edge of the foramen magnum.

E. R. LE COUNT.

POISON STATISTICS. E. R. GRAWITZ and A. WAEGNER, *Ztschr. f. klin. Med.* **106**:783, 1927.

This is a second summary of the poisonings cared for in a single hospital in Berlin. The first appeared as an inaugural dissertation by Beeck in 1925, "Ueber klinische Beobachtungen bei Leuchtgasvergiftungen." In the period covered by the two reports, about fourteen years, the total number of cases of poisoning was 1,135; of these, 842 were due to carbon monoxide. The mortality is not mentioned. Among 703 of the 1,135, there were 331 attempted suicides, 242 by women and 89 by men; only 43 were successful, and 146 were by persons between 20 and 30 years of age. Of 77 poisonings by veronal, only 3 were not suicidal.

The list of alkaloidal poisons, or of poisons with names suggesting alkaloids, is a long one and includes barbital and barbital derivatives, revouerin, dihydrocodeine, pantopium hydrochloricum, quinine, acetyl-salicylic acid and carbonal. It is of interest that no difficulty apparently exists in obtaining these rather unusual drugs when they are desired for suicide, and also that they are responsible for accidental poisoning.

E. R. LE COUNT.

Technical

A NEW SELECTIVE STAINING METHOD FOR THE DEMONSTRATION OF THE GLOMERULAR VASCULAR BED. STUART WILSON, *Warthin Ann.* Vol., 1927, p. 519.

After experimenting with a number of dyes, Wilson considers that a distilled water solution of janus green (1:800) injected into the renal artery after perfusion with physiologic salt solution, gives the best stained preparations of the glomerular-vascular structures. Frozen sections, not cleared, but air dried and mounted in balsam give best results. The method is applicable to kidneys removed surgically, autopsy material and experimental investigations in animals.

WALTER M. SIMPSON.

A NEW SYPHILIS REACTION (MKR.). E. MEINICKE, *Klin. Wchnschr.* **8**:112, 1929.

Meinicke offers another flocculation test for the serum diagnosis of syphilis. For the details of the procedure the original article should be consulted.

EDWIN F. HIRSCH.

REPLACEMENT OF THE SKULL OF THE CADAVER BY A WAX MODEL. L. PICK, *Virchows Arch. f. path. Anat.* **266**:604, 1927.

A method is described for substituting a wax model instead of a plaster one for the skull of the cadaver. This makes a more lifelike appearance possible.

B. R. LOVETT.

A SELECTIVE STAINING METHOD FOR BROWN AND MELANOTIC PIGMENTS. E. P. LASNIER, *Virchows Arch. f. path. Anat.* **266**:693, 1928.

A method (see the original) is described for staining brown pigment, especially in the muscle of the heart, and melanotic pigment in the skin and in tumors. The method enables clear distinction between these and other substances, such as iron-containing blood pigment and bile pigments, which may have the same appearance with ordinary staining methods.

B. R. LOVETT.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Dec. 10, 1928

HENRY C. SWEANY, *Vice-President, in the Chair*

BLOOD CHANGES IN MECHANICAL CONSTRICTION OF THE HEPATIC VEINS. W. W. BRANDES and J. P. SIMONDS.

Two years ago we devised a method of mechanically constricting the hepatic veins in the dog. Briefly stated, this consists in passing a small sized rubber tube through the foramen of Winslow and through the ligamentous attachments of the liver taking care to include all the lobes. The two free ends of the tube are brought up over the surface of the liver and passed through two small holes bored lengthwise in a small flat wooden block. By pulling up on the ends of the tube and at the same time pushing the block downward the hepatic veins can be constricted to any desired degree up to complete obstruction. By placing a clamp on the rubber tube immediately above the block the inferior vena cava is not at all interfered with. By this method the liver can be shut out of the general circulation and returned at will.

The changes in blood pressure induced by this procedure consist of a precipitate fall in arterial pressure of from 40 to 60 mg. of mercury. The pressure reaches a level which is reasonably constant for at least twenty minutes. On release of the hepatic veins, the blood pressure rises immediately to a level usually about 10 mm. higher than before constriction and returns to normal in about one-half minute. This marked fall in arterial pressure is due to the sudden throwing out of the general circulation of the large volume of blood in the liver and branches of the portal vein.

Along with this decrease in blood pressure the flow of lymph from the thoracic duct is markedly increased, an average increase of 5.2 times normal.

Determinations of blood concentration by the method of Lamson and Roca show that a rapid moderate dilution of the blood occurs during the first five minutes of constriction followed by a gradual recovery during the following ten minutes before the hepatic veins are released. The marked increase in flow of lymph from the thoracic duct, and the entrance of fluid into the blood from the tissues as is the case in low blood pressure from hemorrhage are probable factors in this dilution. The reason for the gradual return of concentration to normal is not clear. It may be due to the forcing of a small amount of highly concentrated blood through the constriction as a result of the increased pressure in the liver and to the fact that the lymph in the thoracic duct usually shows red blood cells after the first five minutes of constriction.

The coagulation time in these animals before constriction ranged from two and one-quarter to four and one-half minutes. Constriction of the hepatic veins caused a distinct shortening of the coagulation time, from an average in six dogs of two hundred and ten seconds before constriction to an average of ninety seconds, ten minutes after constriction was applied. No clear explanation is offered for this change, and further studies are being made to determine its cause. It may be that the heparin of the blood is rapidly used up, thus allowing coagulation to occur more readily. There is no satisfactory quantitative test for heparin in the blood. A number of determinations on the quantity of fibrin have been made but as yet not of sufficient number to justify any statement, but there seems to be a decrease when the hepatic veins are constricted. Blood platelets also show a tendency to decrease apparently. Work is to be carried out on calcium and pH determinations.

Mann and others have shown that total removal of the liver results in a fall of blood sugar to such a low level that hypoglycemic convulsions occur. Constriction of the hepatic veins results in a surprisingly rapid fall in the blood sugar. There was an average maximum fall of 42 per cent in fifteen minutes after constriction. As soon as the constriction is released the blood sugar promptly rises to a level considerably higher than that before the veins were constricted. We believe that the marked congestion and stasis in the liver causes a local acidosis which stimulates glycogenolysis, thus liberating sugar in the liver. When the hepatic veins are released, there is delivered to the general circulation a hepatic blood with a high concentration of sugar. We tested several dogs by starving and insulin injection to render the liver glycogen-free. In these the constriction of the hepatic veins caused only slight fluctuations in blood sugar.

DISCUSSION

E. F. HIRSCH: Have measurements been made of the reaction or carbon dioxide combining power of the blood?

W. F. PETERSEN: I have blocked the liver by injecting petroleum into the portal vein, and in twenty minutes noted liver injury. The lymph from the thoracic duct at first was thin, later concentrated. The carbon dioxide combining power at first was increased but later diminished, and some bile appeared in the lymph. Was the concentration of the bile determined?

J. P. SIMONDS: Further studies in answer to the questions asked are in progress.

PRIMARY INTRAHEPATIC THROMBOSIS OF THE PORTAL VEIN. LOUISA HEMKEN BACON.

Most of the reports in the medical literature of the thrombosis of the portal vein which accompanies atrophic cirrhosis of the liver, refer to its origin and subsequent development outside the liver in the large trunk or its right and left branches, and to an extension of the thrombosis out into the liver (Webster, L. T.: Portal Thrombosis, *Bull. Johns Hopkins Hosp.* 32:16, 1921; Quincke, H., and Hoppe-Seyler, G., in Nothnagel: *Encyclopedia of Practical Medicine, Diseases of the Liver and Pancreas, and Suprarenal Glands*, Philadelphia, W. B. Saunders Company, 1905, p. 885). The study I have made is apparently of a contrary course of events, a retrograde thrombosis in the branches of the portal vein from many places far out in the peripheral parts of the liver to the extrahepatic main stem which became secondarily occluded shortly before death.

The patient, a woman, aged 61 years, was admitted to the service of Dr. Lester E. Frankenthal, Sr., in the Michael Reese Hospital, Chicago. The only noteworthy information regarding her previous health was that following the birth of a healthy normal child when she was 39 years of age, her physicians said she had, for a time, suffered from uremia. On admission, she complained of enlargement of the abdomen, dyspnea and cough. The enlarged abdomen was tense so that abdominal organs could not be palpated. The blood count was within normal limits. A trace of albumin was present in the urine, and occult blood was found in the stools on two occasions, on the day of admission and two days later. Examination of the blood revealed 115 mg. of sugar per hundred cubic centimeters, 37 mg. of nonprotein nitrogen and 1.3 mg. of creatinine. While under observation and treatment in the hospital for eighty-two days (until death), there was a slight fever during the afternoon (99.4 to 100.8 F.) for the first two weeks; during the following three weeks there was some fever all the time (99.2 to 100.4 F.), being highest in the afternoon. This increased to from 100 to 103 F., falling only slightly for a short time after the second operation. During the last two days of life, the temperature never went below 102 F., and reached a maximum of 105 F. a few hours before death.

Fluid was removed from the abdomen 8, 36, 37, 52 and 72 days after admission. On the thirty-seventh and fifty-second days, it was obtained at the time of opera-

tions. Altogether $8\frac{3}{4}$ gallons of a milky fluid were removed. The largest amount at the last tapping on the seventy-second day was $2\frac{1}{2}$ gallons; the smallest, at the time of the first operation, was 1 gallon. Fifteen days after admission a diagnosis of sarcoma of the mesentery was made from examination of a small piece of tissue which came away in the fluid.

Exploratory laparotomy was performed thirty-seven days after admission: the omentum was indurated, the liver was atrophic and the peritoneal covering of the small bowel was studded with engorged blood vessels. No tumor tissue was found in the fluid removed at this operation. Epiploexy was done fifteen days later; two days later slight cyanosis and dyspnea were observed. There was a persistent thick discharge from the incision made during the recent laparotomy. Eighteen days after the operation air hunger and marked tightness of the abdomen were present. Coma, involuntary passage of urine and watery feces were observed during the last few days. Death occurred twenty-nine days after the second operation. The clinical diagnosis was cirrhosis of the liver with terminal uremia.

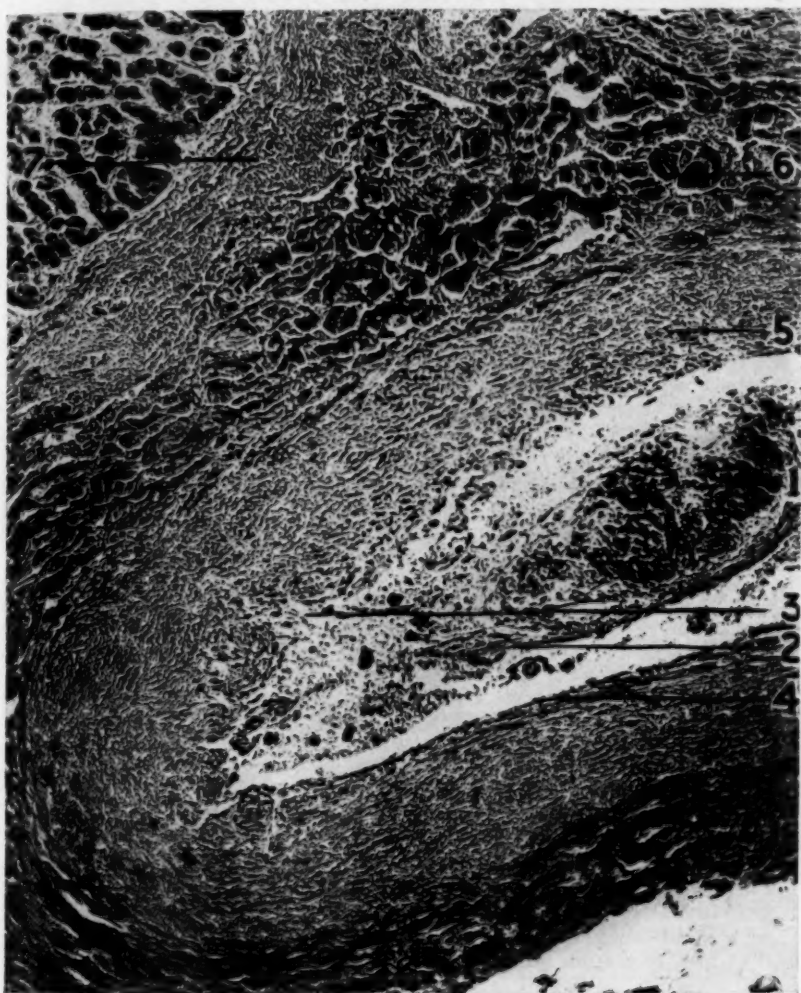
The anatomic diagnosis, made by Dr. E. R. Le Count was: primarily intrahepatic retrograde thrombosis of the portal vein; atrophic cirrhosis of the liver; marked shortening (cyanotic induration) of the small bowel; marked dilation, tortuosity and engorgement of the blood vessels of the peritoneum compensatory to the obstructed portal circulation; chronic indurative epiploitis; recent epiploexy; two recent laparotomy incisions; stitch-abscesses in the subcutaneous fat of the abdomen; hyperplasia of the spleen; markedly distended abdomen; anasarca; slight bronchopneumonia; disseminated superficial atelectasis of the lower lobes of both lungs; bilateral hydrothorax; fatty changes of the kidneys; cloudy swelling of the kidneys and myocardium; minute hemorrhages in the diaphragm, and mucous membranes of the stomach, bowel and renal pelves, and senile arteriosclerosis.

The disease of the liver was typical portal cirrhosis. It was evident from its external appearance that the main branch of the portal vein was thrombosed, for the vessel had a round plump contour. The clot in it was 5.4 cm. in length and about 1 cm. in diameter, forked slightly at the mouths of the splenic and mesenteric veins and adherent ventrally. When detached, a gray spot only a few millimeters in diameter was found in which the vein had lost its normal sheen. The clot was easily followed out into branches of the right lobe of the liver until the channels were not more than 2 mm. in diameter. It did not extend into the left lobe.

Because the thrombus in the main vein possessed all the characteristics of recent formation and the removal of large amounts of fluid from the abdomen had been carried out at rather frequent intervals, a microscopic study was made to learn whether thrombosis of the small branches of the portal vein was generalized throughout the liver. Sections were studied from eighteen places, and partly organized thrombi were found in those from four places in the right and one in the left lobe. Those from the right were 2.6, 4, 7 and 8 cm., respectively from the upper surface; that from the left was 3.6 cm. below. The most peripheral branch thrombosed in these sections was a small vein with a channel from 0.075 to 0.37 mm. in diameter. This was from the piece removed 2.6 cm. below the upper surface of the right lobe. The organization in this branch was more marked than in any of the intrahepatic veins found occluded. The clot in a larger branch 7 cm. below the upper surface of the right lobe was bound fast by considerable granulation tissue at three places in sections obliquely through the vein where the diameter of the channel was from 4 to 7 mm. No clots were found thoroughly organized in any of the sections of the liver.

In the preparations from the large extrahepatic thrombus altogether about 14.3 cm. of contact of thrombus and intima were examined microscopically, and only the earliest changes of fibroblast invasion were found. These occupied only about one twenty fifth of the total junction between clot and vein, and the deepest invasion of the clot was a small triangular mass of fibroblasts and vessels projecting into the clot for a distance equal to only one fourth of the width of the wall of the vein.

In the most peripheral branch of the portal vein containing an organized clot, already described, and with a channel from 0.075 to 0.37 mm. in diameter, the wall is from 0.225 to 0.313 mm. in width. Its adventitia consists of heavy collagen fibers (the sections were stained with phosphotungstic acid hematoxylin) and make up from one half to two thirds of the entire wall of the vein (figure). These are arranged transversely and merge with similar fibers in the outer coat of the adjacent hepatic artery. At other places it appears as if these fibers have pushed



Portal vein containing a thrombus in the right lobe of the liver (from a region 2.6 cm. below the superior margin). 1 indicates fibrin; 2, fibroblasts surrounding fibrin; 3, place of adherence of clot; 4, intima; 5, media; 6, adventitia (collagen fibers); 7, interlobular stroma; $\times 133$.

aside the interlobular fibro-elastic stroma so that there is little of the stroma between the liver cells and portal vein. Definite elastic fibers are between the adventitia and media; the media has smooth muscle and elastic fibers and is from one half to one third of the width of the portal vein. The intima is not thickened.

In the other intrahepatic branches of the portal vein there is a similar change. In some the media has become much narrowed, and the adventitia is particularly wide and prominent. In each section studied from the eighteen different places in the liver, the walls and channels of one or more portal veins were measured. The ratio between the width of the wall and the diameter of the channel was usually 1:1, in a few 1.5:1, and in some of the larger branches 1:4. The channels are narrow compared to the width of the walls. In some veins there are (figure) places in which the wall attains a greater width than the diameter of the channel; in many the two are the same.

The wall of the extrahepatic portion of the portal vein is from 0.125 to 1.20 mm. thick. The adventitia has collagen fibers, but these are not so densely arranged as in the walls of the intrahepatic branches; here they are separated by loose areolar tissue.

The bile ducts about the large intrahepatic branches of the portal vein are heavy due to circularly arranged collagen fibers. They form a broad band about the epithelium of the bile passages about the same width as the adventitia of the adjacent portal veins; in a few they are even greater, reaching a maximum of from 0.4 to 0.5 mm.

The portal cirrhosis was of long standing and was the primary disease. Sclerosis of the portal vein may accompany atrophic cirrhosis (Simmonds, M.: Ueber Pfortadersklerose, *Virchows Arch. f. path. anat.* **207**:360, 1912); the intima is usually much thickened; the media may be wider than normal, and often its elastic fibers are torn. The outstanding characteristic of the thickened portal vein of this report is the marked thickening of the adventitia. This would suggest, together with the thickened walls of the bile duct, that at some time there had been a lymphangitis extending into the liver from the adjacent structures, with subsequent healing and the laying down of collagen fibers about the bile ducts and in the outermost coat of the portal veins within the liver. Syphilis is ordinarily considered to be the prime etiologic factor in sclerosis of the portal vein (Simmonds). It was definitely excluded clinically and from the gross and histologic examination of the liver.

With cirrhosis of the liver, complicated by thrombosis in the stem of the portal vein, ascites develops quickly, and the fluid is disposed to reaccumulate rapidly after tapping (Osler: Principles and Practice of Medicine, ed. 10, New York, D. Appleton & Co., 1925, p. 581). In this patient, fluid collected rapidly in the abdomen when many small intrahepatic branches were occluded and before the thrombosis had extended to the stem of the portal vein. In the gross examination of the liver, the clot in the stem was followed out into branches of the large division of the portal vein for the right lobe of the liver. Histologically, the oldest and most organized clots were found in still smaller vessels with channels from 0.2 to 0.3 mm. wide in both the right and the left lobes; as the portal veins become larger and closer to the hilum, the thrombi are younger in appearance. The smallest and most peripheral branches of the portal vein became occluded first, and the thrombi gradually extended into larger branches against the current. This probably took place during the four or five months just before death; finally thrombosis occurred in the stem of the portal vein, and with its formation, death soon followed. A few textbooks and recent reviews mention the occurrence of retrograde thrombosis. (Stengel, A., and Kern, A.: Nelson Looseleaf Living Medicine, Thomas Nelson and Sons, 1923, vol. 5, p. 521. Delafield, F., and Prudden, T. M.: A Textbook of Pathology, New York, William Wood & Company, 1927, ed. 14, p. 822. Kaspar, F.: Beiträge zur Kenntnis des Verschlusses im Pfortaderstamm und der Vena linealis. Kavernöse Umwandlung der Vena portae und chronisches ulcus duodeni, *Deutsche Ztschr. f. Chir.* **151**:1, 1920.)

Cirrhosis of the liver usually has an afebrile course, although slight rises in temperature for short periods are observed in patients under observation for a long time (Osler). In this patient there was some fever during practically the entire ten weeks before death.

Conclusions: From the histologic examination, it is seen that the first thrombosis occurred far out in the small branches of the portal vein within the liver, and from here extended into the stem. The branches of the portal vein are greatly thickened due primarily to a large amount of collagen in the adventitia, but the media is also thickened. The thickened walls of the bile duct consist of collagen. The deposition of collagen fibers in these two places suggests lymphangitis which may have occurred with the beginning of the cirrhosis.

DISCUSSION

R. H. JAFFE: Thrombi such as these can be traced to the final branches of the portal vein. They are usually seen with chronic or subacute bacterial endocarditis and septicemia. The endothelial cells lining the sinusoids become swollen, and bacteria can be demonstrated in these cells. Then thrombi form, which become larger, and the process spreads toward the hilum. Similar changes occur in the spleen. Were stains or cultures made for bacteria?

H. C. SWEANY: Were there changes in the hepatic veins?

L. H. BACON: No stained slide preparations were made because the tissue changes did not resemble a bacterial infection. The hepatic veins were unchanged.

NEISSERIA SUBFLAVA (BERGEY) MENINGITIS IN AN INFANT. HARRIET BENSON, ROSE BRENNWASSER and DOROTHY D'ANDREA.

The complete report is published in the *Journal of Infectious Diseases* 43:516, 1928.

OSTEOGENIC SARCOMA. ERIC A. FENNEL.

The bone sarcoma registry classifications were discussed, and the need was emphasized for further subclassification of the osteogenic sarcomas. This group has a rather constant character, clinically, roentgenologically, surgically, pathologically and prognostically. A case was reported which must fall into this group, but which deviates in several respects from the typical.

A man, aged 45 years, with multiple exostoses (hereditary) subjected one of these to severe trauma. Within three weeks growth was noted, and in three months the size of the tumor of the femur metaphysis interfered with locomotion. In February, 1923, as much of infiltrating tumor as possible was removed and 2,400 mg. hours of radium were given. The sections contained highly cellular tumor tissue with immature cells and some bone production. A clinical recovery followed. After six years the patient is living and well. The growth seems to be an osteogenic sarcoma.

MULTIPLE HEMANGIOFIBROMAS OF THE PULMONARY VALVE. M. G. BOHROD.

In the body of a man, aged 20 years, dying from multiple brain abscesses, four tumors were found on a leaflet of an otherwise normal pulmonary valve. Microscopically, there were many blood vessels composed of concentric mantles of spindle-shaped cells, without division into layers, and between these there was edematous fibrous tissue and blood pigment. The subintimal elastic tissue of the pulmonary valve was intact and separated the tumors from the valve. These were considered to be true neoplasms, hemangiofibromas.

DISCUSSION

R. H. JAFFE: These tissues are found on the valves and foramen ovale, sites in which there are islets of embryonal tissues. Are they real tumors? I think of them as "hamartomas."

E. F. HIRSCH: The multiplicity of these tissues on the leaflet and the brain abscesses suggest inflammatory origin.

PHILADELPHIA PATHOLOGICAL SOCIETY

Stated Meeting, Jan. 10, 1929

J. HAROLD AUSTIN, *Presiding*GASTRIC ULCER IN A MONKEY (*CERCOPITHECUS CAMPBELLII*). HERBERT FOX.

The specimen presented illustrates several interesting features. While numerous, small, sometimes multiple, ulcers resembling the human peptic ulcer have been encountered in the lower primates, this is the first example of puckering of the gastric wall about the defect, perigastritis with adhesions, obstruction to the antrum pylori and distortion of the duodenum, all features of considerable importance in the human histories. In addition, there was a history of the passage of blood from the mouth and nose. No source for this in the upper alimentary or in the respiratory tract was evident at autopsy, but there was to be seen a vessel end in the floor of the ulcer and there were also some tiny hemorrhages over the fundus of the stomach.

This animal, a fully adult male, had been in the collection for six and one-half years. He was exposed to tuberculosis, contracted the disease and was condemned, but died from weakness caused by the infection and hemorrhages and a generous infestation of *Subulura*.

The only observations of significant connection with the gastric ulcer are as follows: Many teeth were carious. This feature is not mentioned in the protocol of other cases of ulcers in the records. The monkey is prone to have ulcerative gingivitis and cellulitis of the facial tissues; they did not exist in the present case. Carious teeth are common.

The tuberculosis was exclusively abdominal. While the gastric wall was not subject to section, no characters of tuberculosis were seen by gross dissection. The spleen and liver, in which the tuberculous process chiefly existed, were not adherent to the stomach near the ulcer.

What effect the nematodes in the small intestine had on the gastric lesion is entirely speculative. There is one record in our laboratory in which it is evident that a worm of a similar character was coiled in the mucosa about the ulcer. No parasites were found in the stomach in the present case. The following is the description of the specimen as seen at autopsy.

"The stomach is widely distended with gas and contains only a little dull brown fluid. This distention is apparently due to a kink at the pylorus. There are very firm adhesions of the tip of the ascending colon, the omentum and the tip of the gallbladder to the pyloric end of the stomach. This was dissected away, and a scar about 2 by 1 cm. exposed. On opening the stomach a ragged, sharply outlined ulcer with a gray base was exposed. This measures about 1.5 cm. and its lowest extremity is just at the pyloric ring. The mucosa around the pylorus and about 1 inch above it is swollen, pink and edematous. The wall of the rest of the stomach is thin and translucent. The mucosa of the duodenum is swollen, pink and slightly eroded. Below this, the mucosa is flat, pale pink and translucent."

There was a definite ballooning of the cap of the duodenum which section has been pushed and rotated backward until it lay almost on the pancreas and aorta.

The adhesions indicated that penetration of inflammation had taken place, but that a true perforation had occurred cannot be determined. At all events the character and behavior of this ulcer are closely similar to certain occurrences in man, and the growth is the first of its kind I have seen in the wild or domestic animal.

The anatomic basis for this lesion can be the same in the monkey and in man. The micro-anatomy of the two stomachs is essentially the same. The pyloric glands of the monkey are relatively somewhat larger, and they show a greater branching near the surface than do human pyloric glands. The mucosa of the stomach of lower primates is more richly supplied with lymphatic tissue

than is that of man, well formed follicles not infrequently being seen among the gastric tubules. Peptic ulcers of the other lower animals, though rare, are commonest in carnivores and in the abomasum of ungulates. I have never seen the partner of ulcer in crime, cancer, in the same case.

CHEMICAL STUDIES OF GROWTH. FREDERICK S. HAMMETT.

The therapeutic use of lead in malignant disease makes imperative a determination of its action on growing organisms. The detailed report of the studies which have been made at the Research Institute of the Lankenau Hospital, of which this is an abstract, is to be found in *Protoplasma* for 1928-1929.

The test objects used were root-tips grown in culture solutions containing lead as nitrate in various concentrations. *Zea mays*, *Allium cepa* and *Phaseolus vulgaris* seedlings were used. It was found that lead is deposited in the root-tip in the region of most active cell division and that the growth in length of the roots is inhibited. The degree of inhibition runs parallel with the concentration of Pb-ion in the culture solution. Histochemical studies demonstrated that the lead accumulates within the nucleus in high concentration and also in the cell wall. Cell counts showed that mitosis is inhibited by the lead and that this occurs in greater degree the greater the concentration of Pb-ion in the culture solution. The cell size is not adversely affected. Hence, growth here is inhibited because of the inhibition of cell proliferation. It was possible to correlate lead fixation by the nuclei with mitosis, from which the conclusion seems justified that root nuclei in mitosis produce a compound precipitable by lead, and conversely that the inhibition of growth by increase in cell number is due to the throwing out of the field of action of a compound essential for cell division.

Experiments with 3 and 4 day old chick embryos showed that growth is also inhibited here. It is significant that the regions of most active growth by cell proliferation are the very regions in which differential development is most markedly retarded, namely, the head and the somites. This has been reported in the *Journal of Experimental Medicine*, 1928.

THE GRAPHIC METHOD FOR THE BLOOD SEDIMENTATION TEST. JACOB CUTLER.

The blood sedimentation test is one of the newer laboratory procedures striving for a place as a valuable diagnostic aid and prognostic index in infectious and destructive diseases. Although known to physicians for centuries and at one time considered a particularly important clinical sign, both theoretically and practically, its present popularity is due to Fahreus, who, in 1918, introduced it as a diagnostic aid in early pregnancy. More than 650 articles have appeared in the literature since. Many of the early claims have been modified or discarded. Today, no one thinks of the sedimentation test as an early diagnostic procedure in pregnancy or in any disease entity, for the sedimentation reaction is nonspecific.

Evidence is accumulating to show that in the final analysis the sedimentation phenomenon depends on the amount of cellular destruction going on in the body. As the blood circulates from part to part, it carries away products of tissue destruction which alter its stability. In healthy persons, as a result of the wear and tear of everyday life, a certain amount of tissue destruction is always taking place; although this varies from day to day, it remains within limits considered normal. Even this relatively small amount of tissue destruction is registered by the sedimentation test.

Should the amount of tissue destruction pass beyond the normal, then the stability of the blood becomes altered and the red blood cells settle out quickly from the plasma. All the observations recorded in the recent literature emphasize this important fact: regardless of the disease present, whether it is active pulmonary tuberculosis, a malignant condition, pelvic inflammatory disease, acute infections such as typhoid fever, or any disease in which tissue destruction is going on at a greater pace than normal, the rapidity of settling of the red blood cells is in direct proportion to the severity of that disease.

It becomes evident, therefore, that the sedimentation reaction portrays a disturbed function of the blood resulting from destructive disease and should be looked on as one of the fundamental phenomena that occurs during disease and regarded as a measure of pathologic activity in the same sense as fever or leukocytosis. It is often more to be depended on than subjective or objective signs. This does not mean that the sedimentation test is to replace any established procedure or to force to the background sound clinical judgment. On the contrary, if this test is used in conjunction with a temperature chart, examination of the blood, physical examination, history and clinical judgment, it will often cast an additional ray of light on a complex problem and will promote greater confidence in the handling of the sick. The sedimentation test, therefore, should be welcomed.

Three principal methods have been developed for performing this test: the distance, the time and the graphic methods. In the distance method, one fixes the time and measures the distance through which the red cells sediment, recording the results in millimeters, while in the time method one fixes the distance and observes the time, recording the results in minutes.

The graphic method, as the name implies, expresses its results graphically and I have described it in detail in a previous communication (*Am. J. M. Sc.* **171**:882, 1926). Its essential features are as follows:

In the original technic, I used a sedimentation tube of 5 cc. capacity graduated into tenths of a cubic centimeter each 1 mm. in length and marked in millimeters. The graduations began with zero at the 5 cc. level and increased downward to 50.

Further study, however, convinced me that within reasonable limits the quantity of blood used makes little difference. The important thing is to keep the height of the blood column constant. The utilization of this principle enabled me to perfect the finger puncture method (*Am. J. M. Sc.* **173**:687, 1927), and also makes it possible for me to present the following 1 cc. technic, to which I wish to call particular attention.

The only essential apparatus required is a 1 cc. Cutler sedimentation tube. This tube has an internal diameter of 5 mm. and is marked in millimeters, beginning with zero at the 1 cc. level and increasing downward to 50.

Before puncture of the vein, aspirate into the syringe 0.1 cc. of 3 per cent freshly prepared sterile sodium citrate solution, to prevent clotting of the blood. Draw the blood up to the 1 cc. mark and gently mix the blood and the citrate solution by tilting the syringe back and forth, after drawing in a little air. Pour the contents into the sedimentation tube and allow the tube to stand in the carrying rack until ready to make readings.

The test is read by noting the position of the sedimenting column of red blood cells every five minutes for one hour. This is done with ease, as the boundary zone between the red blood cells and the plasma is usually sharp and distinct. The observations are recorded on sedimentation charts, on which the horizontal lines represent the divisions on the sedimentation tube and the vertical lines the intervals of time. A graph is then constructed.

The sedimentation value is determined according to the path traversed by the red blood cells during the first hour and depends on the nature of the graph, the sedimentation index and the sedimentation time, and is the same as when the 5 cc. method is used.

Interpretation of Test.—There are four distinct graphs, two of which are straight lines, and two, curves. From their physical appearance I have named them horizontal line, diagonal line, diagonal curve and vertical curve. The horizontal line is found normally and indicates absence of active destructive disease. It does not, however, exclude the presence of such disease if it is inactive. The sedimentation test merely records the disturbance in the stability of the blood produced by the absorption of products of tissue destruction, and when there is not sufficient tissue destruction, the sedimentation test is normal. The horizontal line, therefore, may indicate one of two things: either health, or the presence of destructive disease not sufficiently active to disturb the natural stability of the blood. The diagonal

line and the diagonal and vertical curves always indicate an abnormal condition and always show the different degrees of the intensity of the destructive process.

For a complete evaluation of the sedimentation test, one must determine two factors in addition to the graph: namely, the sedimentation index and the sedimentation time. These bring out the finer details of the sedimentation reaction and help to determine the degree of activity or quiescence. In this way, they permit comparative study of apparently similar graphs.

By sedimentation time is meant the number of minutes that elapse before the period of packing of the red blood cells sets in. The normal sedimentation time may vary from five to fifteen hours, whereas inflammatory blood may show complete settling in less than thirty minutes. The sedimentation index is the amount of sedimentation at the end of sixty minutes, expressed in millimeters. The normal index for men varies from 2 to 8 mm., and for healthy women, from 2 to 10 mm. As already mentioned, the sedimentation index and sedimentation time help to determine the degree of pathologic activity or quiescence. The greater the index and the shorter the time, the greater is the activity; the smaller the index and the longer the time, the less is the activity.

Advantages of the Graphic Method.—Since the sedimentation test has so many possibilities and is making such a strong bid to become a trusted laboratory aid, it is only fair to request that it should not be hampered by a multiplicity of technics. It is hoped that the following advantages of the graphic method over those in general use will convince many who are interested in the blood sedimentation test that they should use this method:

1. It is scientific. The sedimentation reaction is studied as a natural phenomenon from beginning to end and not within the confines of arbitrary limits.

2. It is complete. It is the only method which permits of a complete study of the sedimentation reaction as it actually occurs in the sedimentation tube.

3. It is delicate. It is the most delicate method that has so far been devised. By means of the graph, sedimentation index and sedimentation time, it reveals all the possible information that the sedimentation reaction can yield.

4. The interpretation is simple. The horizontal line is found normally and indicates either health or the absolute quiescence of destructive disease. The diagonal line and the diagonal and vertical curves show an abnormal condition and always indicate the different degrees of intensity of the destructiveness of the disease.

5. It is graphic. The results are presented graphically and leave a lasting impression on the mind. Improvement or lack of improvement can be dramatically visualized by recording the data of subsequent sedimentation tests on the original chart. As the patient improves the graph should approach more and more the horizontal line, but should he become worse, the vertical curve is more and more in evidence.

6. It is time saving. No observations are made beyond the first hour. In all, only eight readings are essential.

7. It is available under all conditions. The test may be carried out by puncturing either the vein or the finger tip. Venipuncture may be done with either 5 cc. or 1 cc. of citrated blood. The finger puncture method requires less than 0.3 cc. of blood. These methods are interchangeable; they are studied in the same manner and give practically identical results, thus making the sedimentation test available under all conditions. Of these, the 1 cc. technic is the simplest and easiest.

8. It is easy. With the 1 cc. technic described in this article, the sample of blood required can easily be obtained. To read the results of the test, only the average amount of careful observation is required.

VITAMINIZATION OF WHITE WHEAT FLOUR. M. G. WOHL and F. WOOSLEY.

Well marked deficiency diseases as reproduced in animals, such as beriberi and xerophthalmia, are rare in man; symptoms due to chronic vitamin B under-

feeding in man are not uncommon. Loss of appetite (Cowgill), loss of tonicity and irregularity in muscle contracture (Nelson, Balwin and Riggs) and loss of tone of the bowels (Gross) are some of the fundamental effects of food deficient in vitamin B.

The present day American diet, which consists largely of highly refined foods such as degerminated cereals, white flour bread, white rice, lean meats and sugars, has a relative shortage of vitamin B. Vegetables and fruits (cabbage, celery, cauliflower, tomatoes, apricots and apples) which are usually considered rich in vitamin B, show only traces of vitamin B when tested on pigeons. The foregoing mistaken idea has arisen through the fact that these vegetables and fruits were tested in dried form on rats. No human being eats the enormous quantities of these which would be necessary for him to obtain sufficient vitamin B (Plimmer). To enrich a widely used article of human and animal diet with vitamin B appeared a desideratum of importance. White wheat flour in the process of roller milling loses its vitamin B potency. Degerminated wheat flour does not have the tendency to become rancid. It looks whiter and bakes better. Its great biologic disadvantage is that the seat of vitamin B, the germ of the wheat grain, is removed. Experiments in feeding animals with white flour to which a concentrate of 0.5 per cent brewer's yeast was added tended to show the superiority of this over the usual white flour, as it insured constant growth in white rats and prevented polyneuritis in pigeons.

Book Reviews

RECENT ADVANCES IN BACTERIOLOGY (AND THE STUDY OF INFECTION). By J. HENRY DIBLE, Professor of Pathology and Bacteriology in the Welsh National Medical School, Cardiff. Price, \$3.50. Pp. 363, with 22 illustrations. Philadelphia: P. Blakiston's Son & Company, 1929.

In the preface the author states that this book is an attempt by a general reader and student of medical bacteriology to present in a readable form some of the more recent changes in the subject and to indicate the lines on which it is evolving. The period covered is roughly that from the commencement of the war to the beginning of 1928, and within these limits an excellent selection has been made. There are seventeen chapters: the classification of bacteria; the streptococcus problem; bacterial variation; the bacteriophage; experimental epidemiology; Calmette and B.C.G.; ultramicroscopic and filter-passing viruses (3 chapters); diseases associated with Rickettsia bodies; measles and tularemia; recent work on the pneumococci; recent work on spirochetal infections (two chapters); local immunity and the work of Besredka; recent work in connection with diphtheria; recent work on the anaerobic organisms. The first chapter is dismissed with a tabular statement of the various families, tribes and genera selected from Bergey's Manual. The author is of the opinion that this classification will be ultimately accepted by bacteriologists; however, at present this does not appear to be so promising. The streptococcus problem is well presented. The existing controversial nature of this subject is emphasized, but for completeness the work on measles should be mentioned here as well as in the special chapter devoted to measles. The critical reader will be pleased with the chapter on bacterial variation. It is excellent. The author states: "Curious though it may seem, it is nevertheless a fact that such possibilities have been in general rather frowned upon by the great majority of practicing bacteriologists, largely, one assumes, because by excluding their possibility a threatening chaos is kept in the background and a great economy in mental effort is achieved."

The general nature and use of the bacteriophage are carefully considered. The claims of D'Herelle for this agent as a natural therapeutic substance in the cure of disease have been carefully weighed against the data of other workers. In general it may be said that no striking confirmation has been forthcoming. It is logical that the work of Calmette and the B.C.G. should be included in this book, and the author concludes that while the results with B.C.G. are extremely suggestive and of sufficient importance to demand the most careful attention, immediate sweeping deductions from them are to be accepted with the greatest reserve. In the next three chapters a remarkably comprehensive summary of the ultramicroscopic and filter-passing viruses is given. Acute poliomyelitis, encephalitis herpes, encephalitozoon cuniculi, rabies, vaccinia, variola, influenza and the common cold are treated in detail with ten pages devoted to a discussion of the infective theory of malignant diseases. With respect to the latter it cannot be denied that at the present time the matter bears the appearance of the wish begetting the thought. The discussion of the Rickettsia bodies is rather brief but adequate. The author is not at his best in the chapter on measles and tularemia, probably due to the fact that tularemia is the American disease. The pneumococcus problem is well represented; emphasis is given to the contribution from the Rockefeller Institute and to the dissociation work of Griffiths. The author appreciates that the experiments of Griffiths wherein he transforms the various types of the pneumococcus at will should be carefully checked. Under the spirochetal infections the author discusses rat-bite fever, Weil's disease, seven-day fever in Japan, yellow fever and sand-fly fever. The work done on these diseases has been crowded into a short space of time, and there has been little opportunity for an

interchange of experience or material between different workers. Consequently each investigation appears to be somewhat isolated and lacks the mellowing influences of first-hand criticism and suggestion from others engaged in the same field. The vagaries of the spirocheta of syphilis, with respect to its action on the nervous system are mentioned in closing this chapter. The thesis of Besredka is: that the defensive mechanism of the body, in regard to the initial entry of pathogenic organisms, is less an affair of general resistance common to all tissues than a local matter, concentrated in the tissue which is primarily the seat of disease and through which the organism normally gains entry into the body. This view is largely based on experiments with anthrax, but, as a result of other experiments, various workers conclude that the claim of Besredka is to some extent just. The author does not give as extensive a review of the use of Besredka's buccal vaccine as the subject warrants. In fact this criticism may also be applied to the chapter on diphtheria. The discussion of the work of Ramon on the standardizing of diphtheria antitoxin is clear and comprehensive, but the increasing use of anatoxin in place of toxin-antitoxin mixtures for active immunization is scarcely mentioned. The concluding chapter contains a brief review of the various anaerobes. The characteristics of *B. welchii* and its questioned relation to pernicious anemia are emphasized. The reviewer feels that many of the other anaerobes did not gain the recognition that their war activities merit, and objects on the ground of priority to the use of *B. oedematiens* for *B. novyi*. There are a few typographical errors, but on the whole the work of the publisher is highly commendable. The author has accomplished a splendid work, and the book is strongly recommended as an authoritative and a valuable summary of the progress in this field.

MORPHOLOGIC VARIATION AND THE RATE OF GROWTH OF BACTERIA. By Arthur T. Henrici, Professor of Bacteriology, University of Minnesota. (Volume 1 of a series of Monographs on General, Agricultural and Industrial Microbiology, edited by R. E. Buchanan, E. B. Fred and S. A. Waksman). Price, paper \$2.50; cloth \$3.00. Pp. 194, with 36 illustrations and 2 plates. Springfield, Ill.: Charles C. Thomas, 1928.

In the preface the author states that this book makes no pretense of being a treatise on the morphology of bacteria, but is rather a record of personal researches undertaken with the hope that by the "magic of numbers" some order might be brought out of the chaos which has so far filled that field of bacteriology which has to deal with the form and structure of bacterial cells. There are ten chapters, the headings of which indicate the scope of the book: the problem of morphologic variations of bacteria; the rate of growth of bacteria; technic; the size of the cells of *Bacillus megatherium*; the size and form of the cells of the colon bacillus; some observations of a diphtheroid bacillus; a note on spore formation; morphologic variations of the cholera vibrio; senescent forms of the colon bacillus; cytomorphosis in bacteria and an appendix with twenty-seven tables. The first chapter summarizes the observations and hypotheses of such modern pleomorphists as Almquist, Hort, Löhnes, Mellon and Enderlein.

The interpretation on the part of these authors that the presence in pure cultures of cells showing wide variation in size, form and structure proves the existence of life cycles in bacteria is opposed by Henrici. He is convinced that the meagerness and haphazard character of the observations are not consistent with the widespread importance of the conclusions, and that neither the data nor the logic of these new pleomorphists are adequate to convince one that bacteria possess complex fungoid life cycles. In opposition to this theory, the author, after recording measurements of one character or another of nearly 100,000 cells, concludes that variation in bacteria cells occur in a regular and orderly fashion. The variations are not confined to the late stages of growth but occur continually through all stages. Each character reaches its maximum development in some particular phase or at some particular point of inflection of the growth curve. Those factors which cause a variation in the growth rate, vary equally the rate

and degree of change in morphologic characters. The morphologic variations of bacteria are, therefore, an expression of the variation in growth rate.

The reviewer is not in complete sympathy with this interpretation of the data. It is admitted that the failure on the part of those who believe in life-cycles to make continuous observations of all stages of transformation is a just criticism, and, furthermore, the inability to tell whether in particular cases hypotheses or observed facts are being given is also objectionable. However, the reawakened interest in pleomorphism with the accumulation of large amounts of data by unbiased workers may soon interpret for one the real significance of morphologic variation. The book is well printed and bound, and is highly recommended to all who are interested in this fascinating subject.

Books Received

PATHOLOGICO-ANATOMICAL AND CLINICAL INVESTIGATIONS OF FIBRO-ADENOMATOSIS CYSTICA MAMMAE AND ITS RELATION TO OTHER PATHOLOGICAL CONDITIONS IN THE MAMMA, ESPECIALLY CANCER. By Carl Semb. From the Pathologico-Anatomical Institute of the University Hospital, Oslo. Pp. 484. Oslo: Nationaltrykkeriet, 1928.

CHRONIC (NON-TUBERCULOUS) ARTHRITIS. Pathology and Principles of Modern Treatment. By A. G. Timbrell Fisher. Price, \$8.75. Pp. 232, with 186 illustrations. London: H. K. Lewis & Company, Ltd., 1929.

REPORT OF THE INTERNATIONAL CONFERENCE ON CANCER, LONDON, JULY 17-20, 1928. Held under the auspices of the British Empire Cancer Campaign. Price, \$12. Pp. 588. New York: William Wood & Company, 1928.

This fine volume records in full the proceedings of the International Conference on Cancer in July, 1928. The contents include general discussions and papers on the etiology of cancer; the relative values of surgery and radiation in the treatment of cancer; chemotherapeutic treatment with special reference to lead; occupational cancer; early recognition and treatment of cancer of the stomach; sarcoma of bone; cancer cachexia; cancer of the lung; diagnostic methods in relation to cancer; the effects of radium and x-rays on the vascular systems, with special reference to malignant growth, and their biologic effects with reference to wave-length, etc.; the geographic and racial prevalence of cancer, and public action in regard to cancer. The report is of interest to all who try to keep pace with the progress of the study of cancer.

DEGENERATION AND REGENERATION OF THE NERVOUS SYSTEM. By S. Ramon Y. Cajal, M.D., F.R.S., Director of the Instituto Cajal, Madrid; Honorary Professor of Pathology in the University of Madrid. Translated and edited by Raoul M. May, Ph.D. (Harvard), D.Es Sc. (Paris), Laboratoires d'anatomie et histologie comparées et de chimie biologique faculté des sciences, Paris. Two volumes. Pp. 769, with 317 illustrations. London: Oxford University Press, 1928.

LEHRBUCH DER ENTWICKLUNG DES MENSCHEN. Von Dr. Alfred Fischel, O. Professor der Embryologie und Vorstand des Embryologischen Institutes der Wiener Universität. Price, 86 marks. Pp. 822, with 668 illustrations. Berlin: Julius Springer, 1929.

MANSON'S TROPICAL DISEASES. A Manual of the Diseases of Warm Climates. Edited by Philip H. Manson-Bahr, M.D., Physician to the Hospital for Tropical Diseases, London, etc. Ninth edition, revised. Price, \$11. Pp. 921, with 476 illustrations. New York: William Wood and Company, 1929.